THIENOPYRIDINE KINASE INHIBITORS

Technical Field

The present invention relates to compounds which are useful for inhibiting protein tyrosine kinases, methods of making the compounds, compositions containing the compounds, and methods of treatment using the compounds.

Background of the Invention

Protein tyrosine kinases (PTKs) are enzymes which catalyse the phosphorylation of specific tyrosine residues in cellular proteins. This post-translational modification of these substrate proteins, often enzymes themselves, acts as a molecular switch regulating cell proliferation, activation, or differentiation. Aberrant or excessive PTK activity has been observed in many disease states including benign and malignant proliferative disorders as well as diseases resulting from inappropriate activation of the immune system (e.g., autoimmune disorders), allograft rejection, and graft vs. host disease.

Endothelial-cell specific receptor PTKs such as KDR and Tie-2 mediate the angiogenic process, and are thus involved in supporting the progression of cancers and other diseases involving inappropriate vascularization (e.g., diabetic retinopathy, choroidal neovascularization due to age-related macular degeneration, psoriasis, arthritis, retinopathy of prematurity, and infantile hemangiomas).

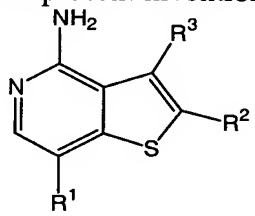
The non-receptor tyrosine kinases represent a collection of cellular enzymes which lack extracellular and transmembrane sequences. At present, over twenty-four individual non-receptor tyrosine kinases, comprising eleven subfamilies (Src, Frk, Btk, Csk, Abl, Zap70, Fes/Fps, Fak, Jak, Ack and LIMK) have been identified. At present, the Src subfamily of non-receptor tyrosine kinases is comprised of the largest number of PTKs and includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk. The Src subfamily of enzymes has been linked to oncogenesis and immune responses.

The identification of effective small compounds which specifically inhibit signal transduction and cellular proliferation by modulating the activity of tyrosine kinases to regulate and modulate abnormal or inappropriate cell proliferation, differentiation, or metabolism is therefore desirable. In particular, the identification of methods and compounds that specifically inhibit the function of a tyrosine kinase which is essential for angiogenic processes or the formation of vascular hyperpermeability leading to edema, ascites, effusions,

exudates, and macromolecular extravasation and matrix deposition as well as associated disorders would be beneficial.

Summary of the Invention

In its principle embodiment, the present invention provides a compound of formula (I)



(I),

or a therapeutically acceptable salt thereof, wherein

R^1 is selected from the group consisting of hydrogen, alkenyl, alkoxyalkynyl, alkoxycarbonylalkenyl, alkoxycarbonylalkyl, alkoxycarbonylalkynyl, alkyl, alkynyl, aryl, arylalkenyl, arylalkyl, arylalkynyl, aryloxyalkyl, aryloxyalkynyl, arylsulfanylalkyl, arylsulfanylalkynyl, carboxyalkenyl, carboxyalkyl, carboxyalkynyl, cyanoalkyl, cyanoalkynyl, cycloalkylalkynyl, formylalkenyl, formylalkyl, halo, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylalkynyl, heteroarylcarbonylalkenyl, heteroarylcarbonylalkyl, heterocyclylalkenyl, heterocyclylalkyl, heterocyclylalkynyl, heterocyclylcarbonylalkenyl, heterocyclylcarbonylalkyl, hydroxyalkenyl, hydroxyalkyl, hydroxyalkynyl, NR^aR^b, (NR^aR^b)alkenyl, (NR^aR^b)alkyl, (NR^aR^b)alkynyl, (NR^aR^b)carbonylalkenyl, (NR^aR^b)carbonylalkyl, (NR^aR^b)carbonylalkynyl, nitro, nitroalkenyl, nitroalkyl, and nitroalkynyl;

R^2 is selected from the group consisting of hydrogen and alkyl;

R^3 is selected from the group consisting of halo, aryl, heteroaryl, and heterocyclyl, wherein the aryl, the heteroaryl, and the heterocyclyl are optionally substituted with one, two, or three substituents independently selected from the group consisting of alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, heteroaryl, heterocyclyl, hydroxy, hydroxyalkyl, LR^4, and NR^aR^b; provided that at least two of the three substituents are other than LR^4;

L is selected from the group consisting of O, $(CH_2)_mC(O)NR^5$, $NR^5C(O)(CH_2)_m$, NR^5SO_2, SO_2NR^5, and $(CH_2)_mN(R^5)C(O)N(R^6)(CH_2)_n$, wherein m and n are independently 0 or 1, and wherein each group is drawn with its right end attached to R^4;

R^4 is selected from the group consisting of aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl; and

R^5 and R^6 are independently selected from the group consisting of hydrogen and alkyl.

In a preferred embodiment the present invention provides the compound of formula (I) wherein R^2 is hydrogen.

In a preferred embodiment the present invention provides the compound of formula (I) wherein R^3 is selected from the group consisting of halo, heteroaryl, and heterocyclyl.

In another preferred embodiment the present invention provides the compound of formula (I) wherein R^3 is aryl.

In another preferred embodiment the present invention provides the compound of formula (I) wherein R^3 is aryl, wherein the aryl is unsubstituted or substituted with one or two substituents independently selected from the group consisting of alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, hydroxyalkyl, and NR^aR^b.

In another preferred embodiment the present invention provides the compound of formula (I) wherein R^3 is aryl, wherein the aryl is substituted with LR^4 and optionally with one or two additional substituents independently selected from the group consisting of alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, hydroxyalkyl, and NR^aR^b.

In a more preferred embodiment the present invention provides the compound of formula (I) wherein R^3 is aryl, wherein the aryl is substituted with LR^4 and optionally with one or two additional substituents independently selected from the group consisting of alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, hydroxyalkyl, and NR^aR^b; and L is O.

In another more preferred embodiment the present invention provides the compound of formula (I) wherein R^3 is aryl, wherein the aryl is substituted with LR^4 and optionally with one or two additional substituents independently selected from the group consisting of alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, hydroxyalkyl, and NR^aR^b; L is O; and R^1 is selected from the group consisting of heterocyclylalkenyl, heterocyclylcarbonylalkenyl, (NR^aR^b)alkenyl, and (NR^aR^b)carbonylalkenyl.

In another more preferred embodiment the present invention provides the compound of formula (I) wherein R^3 is aryl, wherein the aryl is substituted with LR^4 and optionally with one or two additional substituents independently selected from the group consisting of alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, hydroxyalkyl, and NR^aR^b; L is O; and R^1 is selected from the group consisting of hydrogen, alkoxycarbonylalkenyl, carboxyalkenyl, heteroaryl, and hydroxyalkenyl.

In another more preferred embodiment the present invention provides the compound of formula (I) wherein R^3 is aryl, wherein the aryl is substituted with LR^4 and optionally with one or two additional substituents independently selected from the group consisting of alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, hydroxyalkyl, and NR^aR^b; and L is selected from the group consisting of $NR^5C(O)(CH_2)_m$ and NR^5SO_2.

In another more preferred embodiment the present invention provides the compound of formula (I) wherein R^3 is aryl, wherein the aryl is substituted with LR^4 and optionally with one or two additional substituents independently selected from the group consisting of alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, hydroxyalkyl, and NR^aR^b; L is

selected from the group consisting of $NR^5C(O)(CH_2)_m$ and NR^5SO_2; and R^1 is (NR^aR^b)alkenyl.

In another more preferred embodiment the present invention provides the compound of formula (I) wherein R^3 is aryl, wherein the aryl is substituted with LR^4 and optionally with one or two additional substituents independently selected from the group consisting of alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, hydroxyalkyl, and NR^aR^b; L is selected from the group consisting of $NR^5C(O)(CH_2)_m$ and NR^5SO_2; and R^1 is selected from the group consisting of heterocyclylalkenyl, heterocyclylalkyl, and (NR^aR^b)carbonylalkenyl.

In another more preferred embodiment the present invention provides the compound of formula (I) wherein R^3 is aryl, wherein the aryl is substituted with LR^4 and optionally with one or two additional substituents independently selected from the group consisting of alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, hydroxyalkyl, and NR^aR^b; L is selected from the group consisting of $NR^5C(O)(CH_2)_m$ and NR^5SO_2; and R^1 is selected from the group consisting of hydrogen, alkoxycarbonylalkenyl, carboxyalkenyl, formylalkenyl, and heteroaryl.

In another more preferred embodiment the present invention provides the compound of formula (I) wherein R^3 is aryl, wherein the aryl is substituted with LR^4 and optionally with one or two additional substituents independently selected from the group consisting of alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, hydroxyalkyl, and NR^aR^b; L is selected from the group consisting of $NR^5C(O)(CH_2)_m$ and NR^5SO_2; and R^1 is selected from the group consisting of alkoxyalkynyl, arylalkynyl, carboxyalkynyl, cycloalkylalkynyl, halo, heteroarylalkynyl, heterocyclylalkyl, heterocyclylalkynyl, hydroxyalkynyl, and (NR^aR^b)alkynyl.

In another more preferred embodiment the present invention provides the compound of formula (I) wherein R^3 is aryl, wherein the aryl is substituted with LR^4 and optionally with one or two additional substituents independently selected from the group consisting of alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, hydroxyalkyl, and NR^aR^b; and L is $(CH_2)_mN(R^5)C(O)N(R^6)(CH_2)_n$.

In another more preferred embodiment the present invention provides the compound of formula (I) wherein R^3 is aryl, wherein the aryl is substituted with LR^4 and optionally with one or two additional substituents independently selected from the group consisting of alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, hydroxyalkyl, and NR^aR^b; L is $(CH_2)_mN(R^5)C(O)N(R^6)(CH_2)_n$; and R^1 is selected from the group consisting of alkynyl, arylalknyl, aryloxyalkynyl, arylsulfanylalkynyl, cyanoalkynyl, heteroarylalkynyl, hydroxyalkynyl, and (NR^aR^b)alkynyl.

In another more preferred embodiment the present invention provides the compound of formula (I) wherein R^3 is aryl, wherein the aryl is substituted with LR^4 and optionally with

one or two additional substituents independently selected from the group consisting of alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, hydroxyalkyl, and NR^aR^b; L is $(CH_2)_mN(R^5)C(O)N(R^6)(CH_2)_n$; and R^1 is selected from the group consisting of alkoxycarbonylalkenyl, carboxyalkenyl, heteroarylcarbonylalkenyl, heterocyclylcarbonylalkenyl, and (NR^aR^b)carbonylalkenyl.

In another more preferred embodiment the present invention provides the compound of formula (I) wherein R^3 is aryl, wherein the aryl is substituted with LR^4 and optionally with one or two additional substituents independently selected from the group consisting of alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, hydroxyalkyl, and NR^aR^b; L is $(CH_2)_mN(R^5)C(O)N(R^6)(CH_2)_n$; and R^1 is selected from the group consisting of aryl and heteroaryl.

In another more preferred embodiment the present invention provides the compound of formula (I) wherein R^3 is aryl, wherein the aryl is substituted with LR^4 and optionally with one or two additional substituents independently selected from the group consisting of alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, hydroxyalkyl, and NR^aR^b; L is $(CH_2)_mN(R^5)C(O)N(R^6)(CH_2)_n$; and R^1 is selected from the group consisting of alkoxycarbonylalkyl, carboxyalkyl, heterocyclylalkyl, hydroxyalkyl, (NR^aR^b)alkyl, and (NR^aR^b)carbonylalkyl.

In another more preferred embodiment the present invention provides the compound of formula (I) wherein R^3 is aryl, wherein the aryl is substituted with LR^4 and optionally with one or two additional substituents independently selected from the group consisting of alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, hydroxyalkyl, and NR^aR^b; L is $(CH_2)_mN(R^5)C(O)N(R^6)(CH_2)_n$; and R^1 is selected from the group consisting of hydrogen, halo, nitro, and NR^aR^b.

In another preferred embodiment the present invention provides a compound which is (2E)-3-[4-amino-3-(3-phenoxy-1-propynyl)thieno[3,2-*c*]pyridin-7-yl]-*N*-methylacrylamide.

In another preferred embodiment the present invention provides a compound selected from the group consisting of

N-{4-[4-amino-7-(3-pyridinyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(3-methylphenyl)urea;

N-{4-[4-amino-7-(2-methoxy-5-pyrimidinyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-[3-(trifluoromethyl)phenyl]urea;

N-{4-[4-amino-7-(5-pyrimidinyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(3-methylphenyl)urea;

N-(4-{4-amino-7-[3-(diethylamino)-1-propynyl]thieno[3,2-c]pyridin-3-yl}phenyl)-N'-(3-methylphenyl)urea;

N-(4-{4-amino-7-[3-(methylamino)-1-propynyl]thieno[3,2-c]pyridin-3-yl}phenyl)-N'-(3-methylphenyl)urea;

N-{4-[4-amino-7-((1E)-3-{4-[3-(dimethylamino)propyl]-1-piperazinyl}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide;
N-[4-(4-amino-7-{(1E)-3-[4-(aminomethyl)-1-piperidinyl]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide;
1-{(2E)-3-[4-amino-3-(3-methoxy-4-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}phenyl)thieno[3,2-c]pyridin-7-yl]-2-propenyl}-4-piperidinecarboxylic acid;
N-[4-(4-amino-7-{(1E)-3-[trans-(4-aminocyclohexyl)amino]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide; and
N-(4-{4-amino-7-[(1E)-3-(4-amino-1-piperidinyl)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide.

In another preferred embodiment the present invention provides a compound selected from the group consisting of
N-{4-[4-amino-7-(4-pyridinyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea;
N-{4-[4-amino-7-(4-pyridinyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(2-fluoro-5-methylphenyl)urea;
N-(4-{4-amino-7-[(1E)-3-(4-hydroxy-1-piperidinyl)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide; and
N-[4-(4-amino-7-{(1E)-3-[4-(2-hydroxyethyl)-1-piperazinyl]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide.

In another embodiment the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a therapeutically acceptable salt thereof, in combination with a therapeutically acceptable carrier.

In another embodiment the present invention provides a method for inhibiting one or more protein kinases in a patient in recognized need of such treatment comprising administering to the patient a therapeutically acceptable amount of a compound of formula (I), or a therapeutically acceptable salt thereof. Preferably the protein kinases are selected from the group consisting of KDR, Ckit, CSF-1R, PDGFRβ, PDGFRα, Flt-1, Flt-3, Flt-4, Tie-2, Lck, Src, Fyn, Lyn, Blk, Hck, Fgr, Cot, and Yes. More preferably the protein kinases are selected from the group consisting of KDR and Lck.

In another embodiment the present invention provides a method for treating a condition in a patient comprising administering a therapeutically effective amount of a compound of formula (I), or a therapeutically acceptable salt thereof, to the patient, wherein the condition is selected from the group consisting of an ocular condition, a cardiovascular condition, a cancer, Crow-Fukase (POEMS) syndrome, a diabetic condition, sickle cell anemia, chronic imflammation, systemic lupus, glomerulonephritis, synovitis, inflammatory

bowel disease, Crohn's disease, rheumatoid arthritis, osteoarthritis, multiple sclerosis, graft rejection, lyme disease, sepsis, von Hippel Lindau disease, pemphigoid, psoriasis, Paget's disease, polycystic kidney disease, fibrosis, sarcoidosis, cirrhosis, thyroditis, hyperviscosity syndrome, Osler-Weber-Rendu disease, chronic occlusive pulmonary disease, asthma or edema following burns, trauma, radiation, stroke, hypoxia, ischemia, overian hyperstimulation syndrome, preecampsia, menometrorrhagia, endometriosis, or infection by Herpes simplex, Herpes Zoster, human immunodeficiency virus, parapoxyvirus, protozoa, and toxoplasmosis. More preferably the condition is a cancer.

Detailed Description of the Invention

All publications, issued patents, and patent applications cited herein are hereby incorporated by reference.

As used in the present specification the following terms have the meanings indicated:

As used herein, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise.

The term "alkenyl," as used herein, refers to a straight or branched chain group of two to ten carbon atoms containing at least one carbon-carbon double bond. Preferred alkenyl groups of the present invention contain two to three carbon atoms.

The term "alkoxy," as used herein, refers to an alkyl group attached to the parent molecular moiety through an oxygen atom.

The term "alkoxyalkyl," as used herein, refers to an alkyl group substituted with at least one alkoxy group.

The term "alkoxycarbonyl," as used herein, refers to an alkoxy group attached to the parent molecular moiety through a carbonyl group.

The term "alkoxycarbonylalkenyl," as used herein, refers to an alkenyl group substituted with at least one alkoxycarbonyl group.

The term "alkoxycarbonylalkyl," as used herein, refers to an alkyl group substituted with at least one alkoxycarbonyl group.

The term "alkoxycarbonylalkynyl," as used herein, refers to an alkynyl group substituted with at least one alkoxycarbonyl group.

The term "alkyl," as used herein, refers to a group derived from a straight or branched chain saturated hydrocarbon containing from one to ten carbon atoms. Preferred alkyl groups of the present invention contain one to four carbon atoms.

The term "alkylcarbonyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a carbonyl group.

The term "alkylsulfanyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a sulfur atom.

The term "alkylsulfonyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a sulfonyl group.

The term "alkynyl," as used herein, refers to a straight or branched chain hydrocarbon of two to ten carbon atoms containing at least one carbon-carbon triple bond. Preferred alkynyl groups of the present invention contain between two and six carbon atoms.

The term "aryl," as used herein, refers to a phenyl group, or a bicyclic or tricyclic fused ring system wherein one or more of the fused rings is a phenyl group. Bicyclic fused ring systems are exemplified by a phenyl group fused to a monocyclic cycloalkenyl group, as defined herein, a monocyclic cycloalkyl group, as defined herein, or another phenyl group. Tricyclic fused ring systems are exemplified by a bicyclic fused ring system fused to a monocyclic cycloalkenyl group, as defined herein, a monocyclic cycloalkyl group, as defined herein, or another phenyl group. Representative examples of aryl groups include, but are not limited to, anthracenyl, azulenyl, fluorenyl, indanyl, indenyl, naphthyl, phenyl, and tetrahydronaphthyl. The aryl groups of the present invention can be optionally substituted with one, two, three, four, or five substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfanyl, alkynyl, a second aryl group, arylalkenyl, arylalkoxy, arylalkyl, aryloxy, cyano, formyl, halo, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, hydroxy, hydroxyalkyl, nitro, NR^aR^b, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, and oxo; wherein the second aryl group, the aryl part of the arylalkenyl, the arylalkoxy, the arylalkyl, and the aryloxy, the heteroaryl, the heteroaryl part of the heteroarylalkyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl can be further optionally substituted with one, two, three, four, or five substituents independently selected from the group consisting of alkenyl, alkoxy, alkyl, halo, haloalkoxy, haloalkyl, hydroxy, and nitro.

The term "arylalkenyl," as used herein, refers to an alkenyl group substituted with at least one aryl group.

The term "arylalkoxy," as used herein, refers to an arylalkyl group attached to the parent molecular moiety through an oxygen atom.

The term "arylalkoxycarbonyl," as used herein, refers to an arylalkoxy group attached to the parent molecular moiety through a carbonyl group.

The term "arylalkoxycarbonylalkyl," as used herein, refers to an alkyl group substituted with at least one arylalkoxycarbonyl group.

The term "arylalkyl," as used herein, refers to an alkyl group substituted with at least one aryl group.

The term "arylalkynyl," as used herein, refers to an alkynyl group substituted with at least one aryl group.

The term "arylcarbonyl," as used herein, refers to an aryl group attached to the parent

molecular moiety through a carbonyl group.

The term "aryloxy," as used herein, refers to an aryl group attached to the parent molecular moiety through an oxygen atom.

The term "aryloxyalkyl," as used herein, refers to an alkyl group substituted with at least one aryloxy group.

The term "aryloxyalkynyl," as used herein, refers to an alkynyl group substituted with at least one aryloxy group.

The term "arylsulfanyl," as used herein, refers to an aryl group attached to the parent molecular moiety through a sulfur atom.

The term "arylsulfanylalkyl," as used herein, refers to an alkyl group substituted with at least one arylsulfanyl group.

The term "arylsulfanylalkynyl," as used herein, refers to an alkynyl group substituted with at least one arylsulfanyl group.

The term "arylsulfonyl," as used herein, refers to an aryl group attached to the parent molecular moiety through a sulfonyl group.

The term "carbonyl," as used herein, refers to -C(O)-.

The term "carboxy," as used herein, refers to $-CO_2H$.

The term "carboxyalkenyl," as used herein, refers to an alkenyl group substituted with at least one carboxy group.

The term "carboxyalkyl," as used herein, refers to an alkyl group substituted with at least one carboxy group.

The term "carboxyalkynyl," as used herein, refers to an alkynyl group substituted with at least one carboxy group.

The term "cyano," as used herein, refers to -CN.

The term "cyanoalkynyl," as used herein, refers to an alkynyl group substituted with at least one cyano group.

The term "cycloalkenyl," as used herein, refers to a non-aromatic cyclic or bicyclic ring system having three to ten carbon atoms and one to three rings, wherein each five-membered ring has one double bond, each six-membered ring has one or two double bonds, each seven- and eight-membered ring has one to three double bonds, and each nine-to ten-membered ring has one to four double bonds. Representative examples of cycloalkenyl groups include, but are not limited to, cyclohexenyl, octahydronaphthalenyl, and norbornylenyl.

The term "cycloalkyl," as used herein, refers to a saturated monocyclic, bicyclic, or tricyclic hydrocarbon ring system having three to twelve carbon atoms. Representative examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclopentyl, bicyclo[3.1.1]heptyl, and adamantyl. The cycloalkyl groups of the present invention can be

optionally substituted with one, two, three, four, or five substituents independently selected from the group consisting of alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, NR^aR^b, and spiroheterocyclyl. A preferred cycloalkyl group of the present invention is cyclohexyl.

The term "cycloalkylalkyl," as used herein, refers to an alkyl group substituted with at least one cycloalkyl group.

The term "formyl," as used herein, refers to -CHO.

The term "formylalkenyl," as used herein, refers to an alkenyl group substituted with at least one formyl group.

The term "formylalkyl," as used herein, refers to an alkyl group substituted with at least one formyl group.

The terms "halo" and "halogen," as used herein, refer to F, Cl, Br, or I.

The term "haloalkoxy," as used herein, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

The term "haloalkyl," as used herein, refers to an alkyl group substituted by one, two, three, or four halogen atoms. A preferred haloalkyl group of the present invention is trfiluoromethyl.

The term "heteroalkylene," as used herein, refers to a divalent group of two to eight atoms derived from a saturated straight or branched chain containing one or two heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein the remaining atoms are carbon. The heteroalkylene groups of the present invention are attached to the parent molecular moiety through the carbon atoms or the heteroatoms in the chain.

The term "heteroaryl," as used herein, refers to an aromatic five- or six-membered ring where at least one atom is selected from the group consisting of N, O, and S, and the remaining atoms are carbon. The five-membered rings have two double bonds, and the six-membered rings have three double bonds. The heteroaryl groups are connected to the parent molecular moiety through a substitutable carbon or nitrogen atom in the ring. The term "heteroaryl" also includes bicyclic systems where a heteroaryl ring is fused to a phenyl group, a monocyclic cycloalkenyl group, as defined herein, a monocyclic cycloalkyl group, as defined herein, a monocyclic heterocyclyl group, as defined herein, or an additional monocyclic heteroaryl group; and tricyclic systems where a bicyclic system is fused to a phenyl group, a monocyclic cycloalkenyl group, as defined herein, a monocyclic cycloalkyl group, as defined herein, a heterocyclyl group, as defined herein, or an additional monocyclic heteroaryl group. Representative examples of heteroaryl groups include, but are not limited to, benzoxadiazolyl, benzoxazolyl, benzofuranyl, benzothienyl, cinnolinyl, dibenzofuranyl, furanyl, imidazolyl, indazolyl, indolyl, isoxazolyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxadiazolyl, oxadiazolyl, oxazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrazolyl,

pyrrolyl, quinolinyl, thiazolyl, thienopyridinyl, thienyl, triazolyl, thiadiazolyl, and triazinyl. Preferred heteroaryl groups of the present invention are benzofuranyl, benzoxazolyl, furyl, imidazolyl, indolyl, isoquinolinyl, isoxazolyl, pyrazinyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrrolyl, and thienyl. The heteroaryl groups of the present invention can be optionally substituted with one, two, three, four, or five substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfanyl, alkynyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, cyano, formyl, halo, haloalkoxy, haloalkyl, a second heteroaryl group, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, hydroxy, hydroxyalkyl, nitro, NR^aR^b, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, and oxo; wherein the aryl, the aryl part of the arylalkenyl, the arylalkoxy, and the arylalkyl, the second heteroaryl group, the heteroaryl part of the heteroarylalkyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl can be further optionally substituted with one, two, three, four, or five substituents independently selected from the group consisting of alkenyl, alkoxy, alkyl, halo, haloalkoxy, haloalkyl, hydroxy, and nitro.

The term "heteroarylalkenyl," as used herein, refers to an alkenyl group substituted with at least one heteroaryl group.

The term "heteroarylalkyl," as used herein, refers to an alkyl group substituted with at least one heteroaryl group.

The term "heteroarylalkynyl," as used herein, refers to an alkynyl group substituted with at least one heteroaryl group.

The term "heteroarylcarbonyl," as used herein, refers to a heteroaryl group attached to the parent molecular moiety through a carbonyl group.

The term "heteroarylcarbonylalkenyl," as used herein, refers to an alkenyl group substituted with at least one heteroarylcarbonyl group.

The term "heteroarylcarbonylalkyl," as used herein, refers to an alkyl group substituted with at least one heteroarylcarbonyl group.

The term "heterocyclyl," as used herein, refers to a non-aromatic five-, six-, seven-, or eight-membered monocyclic or bicyclic ring where at least one atom is selected from the group consisting of oxygen, nitrogen, and sulfur. The five-membered rings have zero or one double bonds and the six- and seven-membered rings have zero, one, or two double bonds. The heterocyclyl groups of the invention are connected to the parent molecular group through a substitutable carbon or nitrogen atom in the ring. The term "heterocyclyl" also includes systems where a heterocyclyl ring is fused to a phenyl group, a monocyclic cycloalkenyl group, as defined herein, a monocyclic cycloalkyl group, as defined herein, or an additional monocyclic heterocyclyl group; and tricyclic systems where a bicyclic system is fused to a phenyl group, a monocyclic cycloalkenyl group, as defined herein, a monocyclic cycloalkyl group, as defined herein, or an additional monocyclic heterocyclyl group. Representative

examples of heterocyclyl groups include, but are not limited to, benzodioxolyl, benzothiazolyl, dihydroindolyl, dihydropyridinyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxolanyl, isoindolinyl, morpholinyl, piperazinyl, pyrrolidinyl, tetrahydropyridinyl, piperidinyl, and thiomorpholinyl. Preferred heterocyclyl groups of the present invention are benzodioxolyl, diazepinyl, imidazolidinyl, morpholinyl, piperazinyl, piperidinyl, pyrrolidinyl, and tetrahydropyranyl. The heterocyclyl groups of the present invention can be optionally substituted with one, two, three, four, or five substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfanyl, alkynyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, carboxy, carboxyalkyl, cyano, cyanoalkyl, formyl, halo, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkyl, heteroarylcarbonyl, a second heterocyclyl group, heterocyclylalkyl, hydroxy, hydroxyalkyl, nitro, NR^aR^b, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, (NR^aR^b)carbonylalkyl, and oxo; wherein the aryl group, the aryl part of the arylalkenyl, the arylalkoxy, and the arylalkyl, the heteroaryl, the heteroaryl part of the heteroarylalkyl and the heteroarylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl can be further optionally substituted with one, two, three, four, or five substituents independently selected from the group consisting of alkenyl, alkoxy, alkyl, halo, haloalkoxy, haloalkyl, hydroxy, and nitro.

The term "heterocyclylalkenyl," as used herein, refers to an alkenyl group substituted with at least one heterocyclyl group.

The term "heterocyclylalkyl," as used herein, refers to an alkyl group substituted with at least one heterocyclyl group.

The term "heterocyclylalkynyl," as used herein, refers to an alkynyl group substituted with at least one heterocyclyl group.

The term "heterocyclylcarbonyl," as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through a carbonyl group.

The term "heterocyclylcarbonylalkenyl," as used herein, refers to an alkenyl group substituted with at least one heterocyclylcarbonyl group.

The term "heterocyclylcarbonylalkyl," as used herein, refers to an alkyl group substituted with at least one heterocyclylcarbonyl group.

The term "hydroxy," as used herein, refers to -OH.

The term "hydroxyalkenyl," as used herein, refers to an alkenyl group substituted with at least one hydroxy group.

The term "hydroxyalkoxy," as used herein, refers to a hydroxyalkyl group attached to the parent molecular moiety through an oxygen atom.

The term "hydroxyalkoxyalkyl," as used herein, refers to an alkyl group substituted with at least one hydroxyalkoxy group.

The term "hydroxyalkyl," as used herein, refers to an alkyl group substituted with at least one hydroxy group.

The term "hydroxyalkynyl," as used herein, refers to an alkynyl group substituted with at least one hydroxy group.

The term "nitro," as used herein, refers to $-NO_2$.

The term "nitroalkenyl," as used herein, refers to an alkenyl group substituted with at least one nitro group.

The term "nitroalkyl," as used herein, refers to an alkyl group substituted with at least one nitro group.

The term "nitroalkynyl," as used herein, refers to an alkynyl group substituted with at least one nitro group.

The term "NR^aR^b," as used herein, refers to two groups, R^a and R^b, which are attached to the parent molecular moiety through a nitrogen atom. R^a and R^b are independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkoxycarbonylalkyl, arylalkyl, arylcarbonyl, arylsulfonyl, carboxyalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heteroarylcarbonyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxyalkoxyalkyl, hydroxyalkyl, (NR^cR^d)alkyl, (NR^cR^d)carbonyl, and (NR^cR^d)carbonylalkyl, wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkoxycarbonylalkyl, the arylalkyl, the arylcarbonyl, and the arylsulfonyl, the cycloalkyl, the cycloalkyl part of the cycloalkylalkyl, the heteroaryl, the heteroaryl part of the heteroarylalkyl, and the heteroarylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl can be further optionally substituted with one, two, three, four, or five substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, halo, haloalkoxy, haloalkyl, hydroxy, nitro, NR^cR^d, (NR^cR^d)carbonyl, oxo, and spiroheterocyclyl, wherein the aryl and the aryl part of the arylalkyl can be substituted with one, two, three, four, or five substituents independently selected from the group consisting of alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, nitro, and oxo.

The term "(NR^aR^b)alkenyl," as used herein, refers to an alkenyl group substituted with at least one NR^aR^b group.

The term "(NR^aR^b)alkyl," as used herein, refers to an alkyl group substituted with at least one NR^aR^b group.

The term "(NR^aR^b)alkynyl," as used herein, refers to an alkynyl group substituted with at least one NR^aR^b group.

The term "(NR^aR^b)carbonyl," as used herein, refers to an NR^aR^b group attached to the parent molecular moiety through a carbonyl group.

The term "(NR^aR^b)carbonylalkenyl," as used herein, refers to an alkenyl group substituted with at least one (NR^aR^b)carbonyl group.

The term "(NR^aR^b)carbonylalkyl," as used herein, refers to an alkyl group substituted with at least one (NR^aR^b)carbonyl group.

The term "(NR^aR^b)carbonylalkynyl," as used herein, refers to an alkynyl group substituted with at least one (NR^aR^b)carbonyl group.

The term "NR^cR^d," as used herein, refers to two groups, R^c and R^d, which are attached to the parent molecular moiety through a nitrogen atom. R^c and R^d are independently selected from the group consisting of hydrogen, alkyl, aryl, carboxyalkyl, heteroaryl, heterocyclyl, and hydroxyalkyl, wherein the aryl, the heteroaryl, and the heterocyclyl can be optionally substituted with one, two, three, four, or five substituents independently selected from the group consisting of alkenyl, alkoxy, alkyl, halo, haloalkoxy, haloalkyl, hydroxy, and nitro.

The term "(NR^cR^d)alkyl," as used herein, refers to an alkyl group substituted with at least one NR^cR^d group.

The term "(NR^cR^d)carbonyl," as used herein, refers to an NR^cR^d group attached to the parent molecular moiety through a carbonyl group.

The term "(NR^cR^d)carbonylalkyl," as used herein refers to an alkyl group substituted with at least one (NR^cR^d)carbonyl group.

The term "oxo," as used herein, refers to (=O).

The term "spiroheterocyclyl," as used herein, refers to a heteroalkylene diradical, each end of which is attached to the same carbon atom of the parent molecular moiety. Examples of spiroheterocyclyl groups include, but are not limited to, dioxanyl, dioxolanyl, tetrahydrofuranyl, and pyrrolidinyl. The spiroheterocyclyl groups of the present invention can be optionally substituted with one, two, three, or four groups independently selected from the group consisting of alkoxy, alkyl, and halo.

The term "sulfonyl," as used herein, refers to $-SO_2-$.

The compounds of the present invention can exist as therapeutically acceptable salts. The term "therapeutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds of the present invention which are water or oil-soluble or dispersible, which are suitable for treatment of diseases without undue toxicity, irritation, and allergic response; which are commensurate with a reasonable benefit/risk ratio, and which are effective for their intended use. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting an NR^aR^b or NR^cR^d group with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, fumarate,

hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproprionate, picrate, pivalate, propionate, succinate, tartrate, trichloroacetate,trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate, and undecanoate. Also, NR^aR^b and NR^cR^d groups in the compounds of the present invention can be quaternized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diamyl sulfates; decyl, lauryl, myristyl, and steryl chlorides, bromides, and iodides; and benzyl and phenethyl bromides. Examples of acids which can be employed to form therapeutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric.

Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of therapeutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, N,N-dibenzylphenethylamine, 1-ephenamine, and N,N'-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

The present compounds can also exist as therapeutically acceptable prodrugs. The term "therapeutically acceptable prodrug," refers to those prodrugs or zwitterions which are suitable for use in contact with the tissues of patients without undue toxicity, irritation, and allergic response, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use. The term "prodrug," refers to compounds which are rapidly transformed *in vivo* to parent compounds of formula (I) for example, by hydrolysis in blood.

Asymmetric centers exist in the compounds of the present invention. These centers are designated by the symbols "R" or "S," depending on the configuration of substituents around the chiral carbon atom. It should be understood that the invention encompasses all stereochemical isomeric forms, or mixtures thereof, which possess the ability to inhibit one or more protein kinases. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, or

direct separation of enantiomers on chiral chromatographic columns. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art.

Because carbon-carbon double bonds exist in the present compounds, the invention contemplates various geometric isomers and mixtures thereof resulting from the arrangement of substituents around these carbon-carbon double bonds. It should be understood that the invention encompasses both isomeric forms, or mixtures thereof, which possess the ability to inhibit one or more protein kinases. These substituents are designated as being in the E or Z configuration wherein the term "E" represents higher order substituents on opposite sides of the carbon-carbon double bond, and the term "Z" represents higher order substituents on the same side of the carbon-carbon double bond.

It should be understood that the terms "administering a" and "administering to," refer to providing a compound of the present invention to a patient in need of treatment.

The patient to be treated can be any animal, and is preferably a mammal, such as a domesticated animal or a livestock animal. More preferably, the patient is a human.

When it is possible that, for use in therapy, therapeutically effective amounts of a compound of formula (I), as well as therapeutically acceptable salts thereof, may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. Accordingly, the invention further provides pharmaceutical compositions, which include therapeutically effective amounts of compounds of formula (I), or therapeutically acceptable salts thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The compounds of formula (I) and therapeutically acceptable salts thereof are as described above. The carrier(s), diluent(s), or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recepient thereof. In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of formula (I), or a therapeutically acceptable salt thereof, with one or more pharmaceutically acceptable carriers, diluents, or excipients.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain, for example, 0.5mg to 1g, preferably 1mg to 700mg, more preferably 5mg to 100mg of a compound of formula (I), depending on the condition being treated, the severity of the condition, the time of administration, the route of administration, the rate of excretion of the compound employed, the duration of treatment, and the age, gender, weight, and condition of the patient, or pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of an active ingredient per dose. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate

fraction thereof, of an active ingredient. Furthermore, such pharmaceutical formulations may be prepared by any of the methods well known in the pharmacy art.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual, or transdermal), vaginal, or parenteral (including subcutaneous, intramuscular, intravenous, or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil emulsions.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical cerrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing, and coloring agent can also be present.

Capsules are made by preparing a powder mixture, as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate, or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate, or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, wasces, and the like. Lubricants used in these dosage forms include sodium oleate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, betonite, xanthan gum, and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant, and pressing into tablets. A powder mixture is prepared by mixing the compound, suitable comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelating, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or and absorption agent such as betonite, kaolin, or dicalcium phosphate. The powder mixture

can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage, or solutions of cellulosic or polymeric materials and forcing through a screen. As an altenative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc, or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined ith a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material, and a polish coating of wax can be provided. Dyestuffs can be added ot these coatings to distinguis different unit dosages.

Oral fluids such as solution, syrups, and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners, or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or susain the release as for example by coating or embedding particulate material in polymers, wax, or the like.

The compounds of formula (I), and therapeutically acceptable salts thereof, can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

The compounds of formula (I), and therapeutically acceptable salts thereof, may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient

for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols, or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the formulations are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in oil base.

Pharmaceutical formulations adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles, and mouth washes.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a course powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e., by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered, dose pressurized aerosols, nebulizers, or insufflators.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats, and soutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

A therapeutically effective amount of a compound of the present invention will depend upon a number of factors including, for example, the age and weight of the animal, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant physician or veterinarian. However, an effective amount of a compound of formula (I) for the treatment of a protein kinase-mediated condition will generally be in the range of 0.1 to 100 mg/kg body weight of recipient (mammal) per day and more usually in the range of 1 to 10 mg/kg body weight per day.

The compounds of the present invention and therapeutically acceptable salts thereof, may be employed alone or in combination with other therapeutic agents for the treatment of the conditions mentioned herein. For example, in anti-cancer therapy, combination with other chemotherapeutic, hormonal, or antibody agents is envisaged as well as combination with surgical therapy and radiotherapy. Combination therapies according to the present invention thus comprise the administration of at least one compound of formula (I), or a therapeutically acceptable salt thereof, and the use of at least one other cancer treatment method. Preferably, combination therapies according to the present invention comprise the administration of at least one other pharmaceutically active agent, preferably an anti-neoplastic agent. The compound(s) of formula (I) and the other pharmaceutically active agent(s) may be administered together or separately and when administered separately this may occur simultaneously or sequentially in any order. The amounts of the compound(s) of formula (I) and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

The compounds of formula (I), or therapeutically acceptable salts thereof, and at least one additional cancer treatment therapy may be employed in combination concomitantly or sequentially in any therapeutically appropriate combination with such other anti-cancer therapies. In one embodiment, the other anti-cancer therapy is at least one additional chemotherapeutic therapy including administration of at least one anti-neoplastic agent. The administration in combination of a compound of formula (I), or therapeutically acceptable salts thereof, with other anti-neoplastic agents may be in combination in accordance with the invention by administration concomitantly in (1) a unitary pharmaceutical composition including both compounds or (2) separate pharmaceutical compositions each including one of the compounds. Alternatively, the combination may be administered separately in a

sequential manner wherein one anti-neoplastic agent is administered first and the other second or vice versa. Such sequential administration may be close in time or remote in time.

Anti-neoplastic agents may include anti-neoplastic effects in a cell-cycle specific manner, i.e., are phase specific and act at a specific phase of the cell cycle, or bind DNA and act in a non cell-cycle specific manner, i.e., are non-cell cycle specific and operate by other mechanisms.

Anti-neoplastic agents useful in combination with the compounds and salts of formula (I) include the following:

(1) cell cycle specific anti-neoplastic agents including, but not limited to, diterpenoids such as paclitaxel and its analog docetaxel; vinca alkaloids such as vinblastine, vincristine, vindesine, and vinorelbine; epipodophyllotoxins such as etoposide and teniposide; fluoropyrimidines such as 5-fluorouracil and fluorodeoxyuridine; antimetabolites such as allopurinol, fludurabine, methotrexate, cladrabine, cytarabine, mercaptopurine, and thioguanine; and camptothecins such as 9-amino camptothecin, irinotecan, topotecan, CPT-11, and the various optial forms of 7-(-4-methylpiperazino-methylene)-10,11-ethylenedioxy-20-camptothecin;

(2) cytotoxic chemotherapeutic agents including, but not limited to, alkylating agents such as melphalan, chlorambucil, cyclophosphamide, mechlorethamine, hexamethylmelamine, busulfan, carmustine, lomustine, and dacarbazine; anti-tumor antibiotics such as doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dacttainomycin, and mithramycin; and platinum coordination complexes such as cisplatin, carboplatin, and oxaliplatin; and

(3) other chemotherapeutic agents including, but not limited to, anti-estrogens such as tomixefen, toremifene, raloxifene, droloxifene, and iodoxyfene; progesterogens such as megastrol acetate; aromatase inhibitors such as anastrozole, letrazole, vorazole, and exemestane; antiandrogens such as flutamide, nilutamide, bicalutamide, and cyproterone acetate; LHRH agonists and antagonists such as goserelin acetate and luprolide, testosterone 5α-dihydroreductase inhibitors such as finasteride; metallopreteinase inhibitors such as marimastat; antiprogestogens; urokinase plasminogen activator receptor function inhibitors; growth factor function inhibitors such as inhibitors of the functions of hepatocyte growth factor; erb-B2, erb-B4, and epidermal growth factor receptor (EGFR).

In the treatment of immunologic disorders, combination with other agents is also envisaged. Examples of other therapeutic agents include the following: ras inhibitors, anti-IL1 agents, antihistamines, PAF-antagonists, COX-1 inhibitors, COX-2 inhibitors, NO synthase inhibitors, Akt/PTB inhibitors, IGF-1R inhibitors, PKC inhibitors, P13 kinase inhibitors, cyclosporins (e.g., cyclosporin A), CTLA4-Ig, antibodies such as ICAM-3, anti-IL-2 receptor (Anti-Tac), anti-CD45RB, anti-CD2, anti-CD3 (OKT-3), anti-CD4, anti-CD80,

anti-CD86, agents blocking the interaction between CD40 and gp39, such as antibodies specific for CD40 and/or gp39 (i.e., CD154), fusion proteins constructed from CD40 and gp39 (CD40Ig and CD8gp39), inhibitors, such as nuclear translocation inhibitors, of NF-kappa B function, such as deoxyspergualin (DSG), cholesterol biosynthesis inhibitors such as HMG CoA reductase inhibitors (lovastatin and simvastatin), non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and cyclooxygenase inhibitors such as rofecoxib, steroids such as prednisone or dexamethasone, gold compounds, antiproliferative agents such as methotrexate, FK506 (tacrolimus, Prograf), mycophenolate mofetil, cytotoxic drugs such as azathioprine and cyclophosphamide, TNF-alpha inhibitors such as tenidap, anti-TNF antibodies or soluble TNF receptor, and rapamycin (sirolimus or Rapamune) or derivatives thereof. The compound(s) of formula (I) and the other pharmaceutically active agent(s) may be administered together or separately and when administered separately this may occur simultaneously or sequentially in any order. The amounts of the compound(s) of formula (I) and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

Determination of Biological Activity

The *in vitro* potency of compounds in inhibiting these protein kinases may be determined by the procedures detailed below.

The potency of compounds can be determined by the amount of inhibition of the phosphorylation of an exogenous substrate (e.g., synthetic peptide (Z. Songyang *et al.*, *Nature*. 373:536-539) by a test compound relative to control.

KDR Tyrosine Kinase Production Using Baculovirus System:

The coding sequence for the human KDR intra-cellular domain (aa789-1354) was generated through PCR using cDNAs isolated from HUVEC cells. A poly-His6 sequence was introduced at the N-terminus of this protein as well. This fragment was cloned into transfection vector pVL1393 at the Xba 1 and Not 1 site. Recombinant baculovirus (BV) was generated through co-transfection using the BaculoGold Transfection reagent (PharMingen). Recombinant BV was plaque purified and verified through Western analysis. For protein production, SF-9 cells were grown in SF-900-II medium at 2 x 106/ml, and were infected at 0.5 plaque forming units per cell (MOI). Cells were harvested at 48 hours post infection.

Purification of KDR

SF-9 cells expressing $(His)_6$KDR(aa789-1354) were lysed by adding 50 ml of Triton X-100 lysis buffer (20 mM Tris, pH 8.0, 137 mM NaCl, 10% glycerol, 1% Triton X-100, 1mM PMSF, 10µg/ml aprotinin, 1 µg/ml leupeptin) to the cell pellet from 1L of cell culture.

The lysate was centrifuged at 19,000 rpm in a Sorval SS-34 rotor for 30 min at 4 °C. The cell lysate was applied to a 5 ml $NiCl_2$ chelating sepharose column, equilibrated with 50 mM HEPES, pH7.5, 0.3 M NaCl. KDR was eluted using the same buffer containing 0.25 M imidazole. Column fractions were analyzed using SDS-PAGE and an ELISA assay (below) which measures kinase activity. The purified KDR was exchanged into 25mM HEPES, pH7.5, 25mM NaCl, 5 mM DTT buffer and stored at -80 °C.

Human Tie-2 Kinase Production and Purification

The coding sequence for the human Tie-2 intra-cellular domain (aa775-1124) was generated through PCR using cDNAs isolated from human placenta as a template. A poly-His_6 sequence was introduced at the N-terminus and this construct was cloned into transfection vector pVL 1939 at the Xba 1 and Not 1 site. Recombinant BV was generated through co-transfection using the BaculoGold Transfection reagent (PharMingen). Recombinant BV was plaque purified and verified through Western analysis. For protein production, SF-9 insect cells were grown in SF-900-II medium at 2 x 106/ml, and were infected at MOI of 0.5. Purification of the His-tagged kinase used in screening was analogous to that described for KDR.

Human Flt-1 Tyrosine Kinase Production and Purification

The baculoviral expression vector pVL1393 (Phar Mingen, Los Angeles, CA) was used. A nucleotide sequence encoding poly-His6 was placed 5' to the nucleotide region encoding the entire intracellular kinase domain of human Flt-1 (amino acids 786-1338). The nucleotide sequence encoding the kinase domain was generated through PCR using cDNA libraries isolated from HUVEC cells. The histidine residues enabled affinity purification of the protein as a manner analogous to that for KDR and ZAP70. SF-9 insect cells were infected at a 0.5 multiplicity and harvested 48 hours post infection.

EGFR Tyrosine Kinase Source

EGFR was purchased from Sigma (Cat # E-3641; 500 units/50 µL) and the EGF ligand was acquired from Oncogene Research Products/Calbiochem (Cat # PF011-100).

Expression of ZAP70

The baculoviral expression vector used was pVL1393. (Pharmingen, Los Angeles, Ca.) The nucleotide sequence encoding amino acids M(H)6 $LVPR_9S$ was placed 5' to the region encoding the entirety of ZAP70 (amino acids 1-619). The nucleotide sequence encoding the ZAP70 coding region was generated through PCR using cDNA libraries isolated from Jurkat immortalized T-cells. The histidine residues enabled affinity purification of the

protein (vide infra). The $LVPR_9S$ bridge constitutes a recognition sequence for proteolytic cleavage by thrombin, enabling removal of the affinity tag from the enzyme. SF-9 insect cells were infected at a multiplicity of infection of 0.5 and harvested 48 hours post infection.

Extraction and purification of ZAP70

SF-9 cells were lysed in a buffer consisting of 20 mM Tris, pH 8.0, 137 mM NaCl, 10% glycerol, 1% Triton X-100, 1 mM PMSF, 1 μg/ml leupeptin, 10 μg/ml aprotinin and 1 mM sodium orthovanadate. The soluble lysate was applied to a chelating sepharose HiTrap column (Pharmacia) equilibrated in 50 mM HEPES, pH 7.5, 0.3 M NaCl. Fusion protein was eluted with 250 mM imidazole. The enzyme was stored in buffer containing 50 mM HEPES, pH 7.5, 50 mM NaCl and 5 mM DTT.

Protein kinase source

Lck, Fyn, Src, Blk, Csk, and Lyn, and truncated forms thereof may be commercially obtained (e.g., from Upstate Biotechnology Inc. (Saranac Lake, N.Y) and Santa Cruz Biotechnology Inc. (Santa Cruz, Ca.)) or purified from known natural or recombinant sources using conventional methods.

Enzyme Linked Immunosorbent Assay (ELISA) For PTKs

Enzyme linked immunosorbent assays (ELISA) were used to detect and measure the presence of tyrosine kinase activity. The ELISA were conducted according to known protocols which are described in, for example, Voller, *et al.*, 1980, "Enzyme-Linked Immunosorbent Assay," In: *Manual of Clinical Immunology, 2d ed.*, edited by Rose and Friedman, pp 359-371 Am. Soc. of Microbiology, Washington, D.C.

The disclosed protocol was adapted for determining activity with respect to a specific PTK. For example, preferred protocols for conducting the ELISA experiments is provided below. Adaptation of these protocols for determining a compound's activity for other members of the receptor PTK family, as well as non-receptor tyrosine kinases, are well within the abilities of those in the art. For purposes of determining inhibitor selectivity, a universal PTK substrate (e.g., random copolymer of poly(Glu_4 Tyr), 20,000-50,000 MW) was employed together with ATP (typically 5 μM) at concentrations approximately twice the apparent Km in the assay.

The following procedure was used to assay the inhibitory effect of compounds of this invention on KDR, Flt-1, Flt-4, Tie-1, Tie-2, EGFR, FGFR, PDGFR, IGF-1-R, c-Met, Lck, hck, Blk, Csk, Src, Lyn, fgr, Fyn and ZAP70 tyrosine kinase activity:

Buffers and Solutions:

PGTPoly (Glu,Tyr) 4:1

Store powder at -20 °C. Dissolve powder in phosphate buffered saline (PBS) for 50mg/ml solution. Store 1ml aliquots at -20 °C. When making plates dilute to 250µg/ml in Gibco PBS.

Reaction Buffer: 100mM Hepes, 20mM $MgCl_2$, 4mM $MnCl_2$, 5mM DTT, 0.02%BSA, 200µM $NaVO_4$, pH 7.10

ATP: Store aliquots of 100mM at -20 °C. Dilute to 20µM in water

Washing Buffer: PBS with 0.1% Tween 20

Antibody Diluting Buffer: 0.1% bovine serum albumin (BSA) in PBS

TMB Substrate: mix TMB substrate and Peroxide solutions 9:1 just before use or use K-Blue Substrate from Neogen

Stop Solution: 1M Phosphoric Acid

Procedure

1. Plate Preparation:

Dilute PGT stock (50mg/ml, frozen) in PBS to a 250µg/ml. Add 125µl per well of Corning modified flat bottom high affinity ELISA plates (Corning #25805-96). Add 125µl PBS to blank wells. Cover with sealing tape and incubate overnight 37°C. Wash 1x with 250µl washing buffer and dry for about 2hrs in 37°C dry incubator.

Store coated plates in sealed bag at 4°C until used.

2. Tyrosine Kinase Reaction:

-Prepare inhibitor solutions at a 4x concentration in 20% DMSO in water.

-Prepare reaction buffer

-Prepare enzyme solution so that desired units are in 50µl, e.g. for KDR make to 1 ng/µl for a total of 50ng per well in the reactions. Store on ice.

-Make 4x ATP solution to 20µM from 100mM stock in water. Store on ice

-Add 50µl of the enzyme solution per well (typically 5-50 ng enzyme/well depending on the specific activity of the kinase)

-Add 25µl 4x inhibitor

-Add 25µl 4x ATP for inhibitor assay

-Incubate for 10 minutes at room temperature

-Stop reaction by adding 50µl 0.05N HCl per well

-Wash plate

**Final Concentrations for Reaction: 5µM ATP, 5% DMSO

3. Antibody Binding

-Dilute 1mg/ml aliquot of PY20-HRP (Pierce) antibody(a phosphotyrosine antibody)to 50ng/ml in 0.1% BSA in PBS by a 2 step dilution (100x, then 200x)

-Add 100µl Ab per well. Incubate 1 hr at room temp. Incubate 1hr at 4 °C.

-Wash 4x plate

4. Color reaction

-Prepare TMB substrate and add 100µl per well

-Monitor OD at 650nm until 0.6 is reached

-Stop with 1M Phosphoric acid. Shake on plate reader.

-Read OD immediately at 450nm

Optimal incubation times and enzyme reaction conditions vary slightly with enzyme preparations and are determined empirically for each lot.

For Lck, the Reaction Buffer utilized was 100 mM MOPSO, pH 6.5, 4 mM $MnCl_2$, 20 mM $MgCl_2$, 5 mM DTT, 0.2% BSA, 200 mM $NaVO_4$ under the analogous assay conditions.

Representative compounds of examples 1-174, 275-280, and 284-293 inhibited KDR at IC_{50} values between about 0.004 µM and about 50 µM. Preferred compound inhibited KDR at IC_{50} values between about 0.004 µM and about 1.5 µM.

Representative compounds of examples 175-274, 281-283, and 294-420 inhibited Lck at IC_{50} values between about 0.06 µM and about 50 µM. Preferred compound inhibited Tie-2 at IC_{50} values between about 0.06 µM and about 1.0 µM.

Compounds of the present invention may have therapeutic utility in the treatment of diseases involving both identified, including those mentioned and unmentioned herein, and as yet unidentified protein tyrosine kinases. Examples of protein kinases include, but are not limited to, KDR, Ckit, CSF-1R, PDGFRβ, PDGFRα, Flt-1, Flt-3, Flt-4, Tie-2, Lck, Src, Fyn, Lyn, Blk, Hck, Fgr, Cot, and Yes.

Cdc2 source

The human recombinant enzyme and assay buffer may be obtained commercially (New England Biolabs, Beverly, MA. USA) or purified from known natural or recombinant sources using conventional methods.

Cdc2 Assay

A protocol that can be used is that provided with the purchased reagents with minor modifications. In brief, the reaction is carried out in a buffer consisting of 50mM Tris pH 7.5, 100mM NaCl, 1mM EGTA, 2mM DTT, 0.01% Brij, 5% DMSO and 10mM $MgCl_2$ (commercial buffer) supplemented with fresh 300 µM ATP (31 µCi/ml) and 30 µg/ml histone type IIIss final concentrations. A reaction volume of 80µL, containing units of enzyme, is run for 20 minutes at 25 degrees C in the presence or absence of inhibitor. The reaction is terminated by the addition of 120µL of 10% acetic acid. The substrate is separated from unincorporated label by spotting the mixture on phosphocellulose paper, followed by 3

washes of 5 minutes each with 75mM phosphoric acid. Counts are measured by a betacounter in the presence of liquid scintillant.

PKC kinase source

The catalytic subunit of PKC may be obtained commercially (Calbiochem).

PKC kinase assay

A radioactive kinase assay is employed following a published procedure (Yasuda, I., Kirshimoto, A., Tanaka, S., Tominaga, M., Sakurai, A., Nishizuka, Y. *Biochemical and Biophysical Research Communication 3*:166, 1220-1227 (1990)). Briefly, all reactions are performed in a kinase buffer consisting of 50 mM Tris-HCl pH7.5, 10mM $MgCl_2$, 2mM DTT, 1mM EGTA, 100 μM ATP, 8 μM peptide, 5% DMSO and ^{33}P ATP (8Ci/mM). Compound and enzyme are mixed in the reaction vessel and the reaction is initiated by addition of the ATP and substrate mixture. Following termination of the reaction by the addition of 10 μL stop buffer (5 mM ATP in 75mM phosphoric acid), a portion of the mixture is spotted on phosphocellulose filters. The spotted samples are washed 3 times in 75 mM phosphoric acid at room temperature for 5 to 15 minutes. Incorporation of radiolabel is quantified by liquid scintillation counting.

Erk2 enzyme source

The recombinant murine enzyme and assay buffer may be obtained commercially (New England Biolabs, Beverly MA. USA) or purified from known natural or recombinant sources using conventional methods.

Erk2 enzyme assay

In brief, the reaction is carried out in a buffer consisting of 50 mM Tris pH 7.5, 1mM EGTA, 2mM DTT, 0.01% Brij, 5% DMSO and 10 mM $MgCl_2$ (commercial buffer) supplemented with fresh 100 μM ATP (31 μCi/ml) and 30μM myelin basic protein under conditions recommended by the supplier. Reaction volumes and method of assaying incorporated radioactivity are as described for the PKC assay (vide *supra*).

Cellular Receptor PTK Assays

The following cellular assay was used to determine the level of activity and effect of the different compounds of the present invention on KDR/VEGFR2. Similar receptor PTK assays employing a specific ligand stimulus can be designed along the same lines for other tyrosine kinases using techniques well known in the art.

VEGF-Induced KDR Phosphorylation in Human Umbilical Vein Endothelial Cells (HUVEC) as Measured by Western Blots:

1. HUVEC cells (from pooled donors) can be purchased from Clonetics (San Diego, CA) and cultured according to the manufacturer directions. Only early passages (3-8) are used for this assay. Cells are cultured in 100 mm dishes (Falcon for tissue culture; Becton Dickinson; Plymouth, England) using complete EBM media (Clonetics).

2. For evaluating a compound's inhibitory activity, cells are trypsinized and seeded at 0.5-1.0 x 10^5 cells/well in each well of 6-well cluster plates (Costar; Cambridge, MA).

3. 3-4 days after seeding, plates are typically 90-100% confluent. Medium is removed from all the wells, cells are rinsed with 5-10ml of PBS and incubated 18-24h with 5ml of EBM base media with no supplements added (i.e., serum starvation).

4. Serial dilutions of inhibitors are added in 1ml of EBM media (25μM, 5μM, or 1μM final concentration to cells and incubated for one hour at 37 °C. Human recombinant $VEGF_{165}$ (R & D Systems) is then added to all the wells in 2 ml of EBM medium at a final concentration of 50ng/ml and incubated at 37 °C for 10 minutes. Control cells untreated or treated with VEGF only are used to assess background phosphorylation and phosphorylation induction by VEGF.

All wells are then rinsed with 5-10ml of cold PBS containing 1mM Sodium Orthovanadate (Sigma) and cells are lysed and scraped in 200μl of RIPA buffer (50mM Tris-HC1) pH7, 150mM NaCl, 1% NP-40, 0.25% sodium deoxycholate, 1mM EDTA) containing protease inhibitors (PMSF 1mM, aprotinin 1μg/ml, pepstatin 1μg/ml, leupeptin 1μg/ml, Na vanadate 1mM, Na fluoride 1mM) and 1μg/ml of Dnase (all chemicals from Sigma Chemical Company, St Louis, MO). The lysate is spun at 14,000 rpm for 30min, to eliminate nuclei.

Equal amounts of proteins are then precipitated by addition of cold (-20 °C) Ethanol (2 volumes) for a minimum of 1 hour or a maximum of overnight. Pellets are reconstituted in Laemli sample buffer containing 5% -mercaptoethanol (BioRad; Hercules, CA) and boiled for 5min. The proteins are resolved by polyacrylamide gel electrophoresis (6%, 1.5mm Novex, San Deigo, CA) and transferred onto a nitrocellulose membrane using the Novex system. After blocking with bovine serum albumin (3%), the proteins are probed overnight with anti-KDR polyclonal antibody (C20, Santa Cruz Biotechnology; Santa Cruz, CA) or with anti-phosphotyrosine monoclonal antibody (4G10, Upstate Biotechnology, Lake Placid, NY) at 4 °C. After washing and incubating for 1 hour with HRP-conjugated $F(ab)_2$ of goat anti-rabbit or goat-anti-mouse IgG the bands are visualized using the emission chemiluminescience (ECL) system (Amersham Life Sciences, Arlington Heights, IL).

In vivo Uterine Edema Model

This assay measures the capacity of compounds to inhibit the acute increase in uterine weight in mice which occurs in the first few hours following estrogen stimulation. This early onset of uterine weight increase is known to be due to edema caused by increased permeability of uterine vasculature. Cullinan-Bove and Koss (*Endocrinology* (1993), *133*:829-837) demonstrated a close temporal relationship of estrogen-stimulated uterine edema with increased expression of VEGF mRNA in the uterus. These results have been confirmed by the use of neutralizing monoclonal antibody to VEGF which significantly reduced the acute increase in uterine weight following estrogen stimulation (WO 97/42187). Hence, this system can serve as a model for *in vivo* inhibition of VEGF signalling and the associated hyperpermeability and edema.

Materials: All hormones can be purchased from Sigma (St. Louis, MO) or Cal Biochem (La Jolla, CA) as lyophilized powders and prepared according to supplier instructions. Vehicle components (DMSO, Cremaphor EL) can be purchased from Sigma (St. Louis, MO). Mice (Balb/c, 8-12 weeks old) can be purchased from Taconic (Germantown, NY) and housed in a pathogen-free animal facility in accordance with institutional Animal Care and Use Committee Guidelines.

Method:

Day 1: Balb/c mice are given an intraperitoneal (i.p.) injection of 12.5 units of pregnant mare's serum gonadotropin (PMSG).

Day 3: Mice receive 15 units of human chorionic gonadotropin (hCG) i.p.

Day 4: Mice are randomized and divided into groups of 5-10. Test compounds are administered by i.p., i.v. or p.o. routes depending on solubility and vehicle at doses ranging from 1-100 mg/kg. Vehicle control group receive vehicle only and two groups are left untreated.

Thirty minutes later, experimental, vehicle and 1 of the untreated groups are given an i.p. injection of 17 -estradiol (500 mg/kg). After 2-3 hours, the animals are sacrificed by CO_2 inhalation. Following a midline incision, each uterus was isolated and removed by cutting just below the cervix and at the junctions of the uterus and oviducts. Fat and connective tissue were removed with care not to disturb the integrity of the uterus prior to weighing (wet weight). Uteri are blotted to remove fluid by pressing between two sheets of filter paper with a one liter glass bottle filled with water. Uteri are weighed following blotting (blotted weight). The difference between wet and blotted weights is taken as the fluid content of the uterus. Mean fluid content of treated groups is compared to untreated or vehicle treated groups. Significance is determined by Student's test. Non-stimulated control group is used to monitor estradiol response.

Certain compounds of this invention which are inhibitors of angiogenic receptor tyrosine kinases can also be shown active in a Matrigel implant model of neovascularization.

The Matrigel neovascularization model involves the formation of new blood vessels within a clear marble of extracellular matrix implanted subcutaneously which is induced by the presence of proangiogenic factor producing tumor cells (for examples see: Passaniti, A., *et al*, Lab. Investig. (1992), 67(4), 519-528; Anat. Rec. (1997), 249(1), 63-73; Int. J. Cancer (1995), 63(5), 694-701; Vasc. Biol. (1995), 15(11), 1857-6). The model preferably runs over 3-4 days and endpoints include macroscopic visual/image scoring of neovascularization, microscopic microvessel density determinations, and hemoglobin quantitation (Drabkin method) following removal of the implant versus controls from animals untreated with inhibitors. The model may alternatively employ bFGF or HGF as the stimulus.

The compounds of the present invention may be used in the treatment of protein kinase-mediated conditions, such as benign and neoplastic proliferative diseases and disorders of the immune system. Such diseases include autoimmune diseases, such as rheumatoid arthritis, thyroiditis, type 1 diabetes, multiple sclerosis, sarcoidosis, inflammatory bowel disease, Crohn's disease, myasthenia gravis and systemic lupus erythematosus; psoriasis, organ transplant rejection (e.g,. kidney rejection, graft versus host disease), benign and neoplastic proliferative diseases, human cancers such as lung, breast, stomach, bladder, colon, pancreatic, ovarian, prostate and rectal cancer and hematopoietic malignancies (leukemia and lymphoma), glioblastoma, infantile hemangioma, and diseases involving inappropriate vascularization (for example diabetic retinopathy, retinopathy of prematurity, choroidal neovascularization due to age-related macular degeneration, and infantile hemangiomas in human beings). Such inhibitors may be useful in the treatment of disorders involving VEGF mediated edema, ascites, effusions, and exudates, including for example macular edema, cerebral edema, acute lung injury and adult respiratory distress syndrome (ARDS). In addition, the compounds of the invention may be useful in the treatment of pulmonary hypertension, particularly in patients with thromboembolic disease (*J. Thorac. Cardiovasc. Surg.* 2001, 122 (1), 65-73).

Synthetic Methods

Abbreviations which have been used in the descriptions of the scheme and the examples that follow are: LDA for lithium diisopropylamide; DMF for N,N-dimethylformamide; dppf for diphenylphosphinoferrocene; PPh_3 for triphenylphosphine; DMSO for dimethylsulfoxide; TFA for trifluoroacetic acid; HOBT for 1-hydroxybenzotriazole; EDCI for 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide; THF for tetrahydrofuran; DME for 1,2-dimethoxyethane; Et_3N for triethylamine; TBTU for O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate; OAc for acetate; DIBAL-H for diisobutylaluminum hydride; HBTU for O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate; and BOC for tert-butoxycarbonyl.

The compounds and processes of the present invention will be better understood in connection with the following synthetic schemes which illustrate the methods by which the compounds of the invention may be prepared. Starting materials can be obtained from commercial sources or prepared by well-established literature methods known to those of ordinary skill in the art.

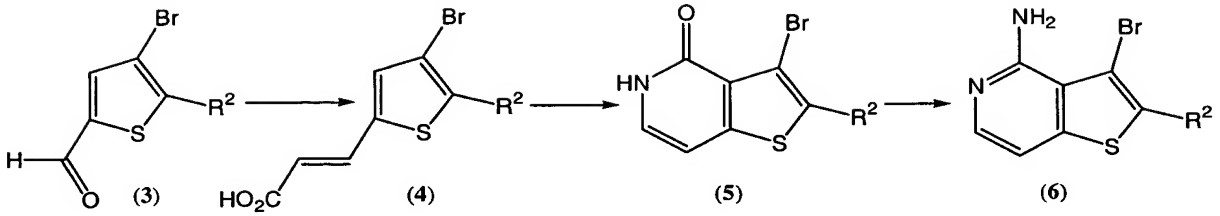
The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention.

It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene and Wuts (Protective Groups In Organic Synthesis, Wiley and Sons, 1999). Suitable protecting groups include, but are not limited to, tert-butoxycarbonyl (BOC), trimethylsilylethanesulfonamide (SES), benzyloxycarbonyl (CBZ) and benzyl (Bn) protecting groups. The BOC protecting group may be removed by treatment with an acid such as trifluoroacetic acid or concentrated hydrochloric acid and the SES protecting group may be removed with a fluoride salt, such as cesium fluoride or tetrabutylammonium fluoride. The CBZ and Bn protection groups may be removed by catalytic hydrogenation. Additional suitable protecting groups for hydroxy substituents include, but are not limited to, t-butyldimethylsilyl (TBDMS), tetra-hydropyranyl (THP), or isopropyl (i-Pr) protecting groups. The TBDMS and THP protecting groups may be removed by treatment with an acid such as acetic acid or hydrochloric acid while the i-Pr protecting group may be removed by aluminum trichloride.

This invention is intended to encompass compounds having formula (I) when prepared by synthetic processes or by metabolic processes. Preparation of the compounds of the invention by metabolic processes include those occurring in the human or animal body (*in vivo*) or processes occurring *in vitro*.

The groups R^1,R^2, R^3, R^4, and R^5 are as defined above unless otherwise noted below.

Scheme 1



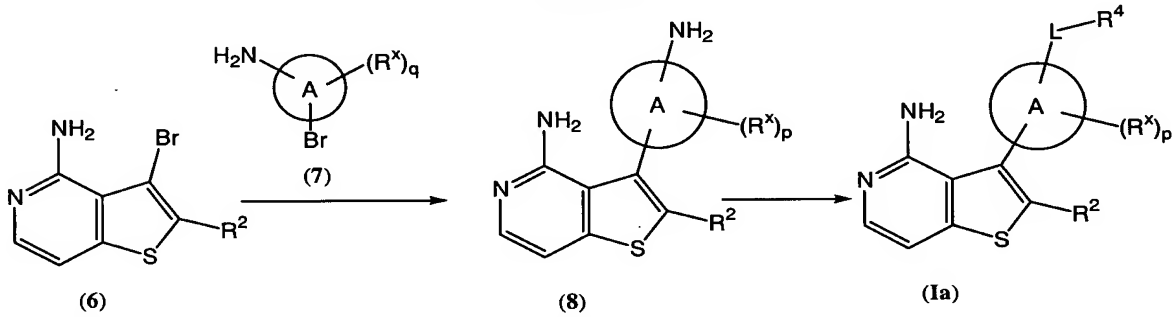
Scheme 1 shows the synthesis of compounds of formula (**6**). Compounds of formula (**3**) can be reacted with ethyl (diethoxyphosphino)acetate in the presence of a base such as sodium hydride, LDA, or lithium hexamethyldisilazide to provide compounds of formula (**4**). This reaction is typically conducted at about 0 to about 25 °C for about 1 to about 6 hours.

Alternatively, compounds of formula (**3**) can be treated with malonic acid in the presence of pyridine and piperidine to provide compounds of formula (**4**). The reaction is typically conducted at about 90 to about 110 °C for abou 6 to about 18 hours.

Compounds of formula (**4**) can be converted to compounds of formula (**5**) by treatment with thionyl chloride and DMF followed by treatment with sodium azide and subsequent heating. The reaction is conducted at about 30 to about 260 °C for about 5 to about 10 hours.

Conversion of compounds of formula (**5**) to compounds of formula (**6**) can be accomplished by treatment with $POCl_3$ at about 108 °C for about 1 to about 4 hours followed by treatment with ammonia under pressure at about 140 to about 160 °C.

Scheme 2

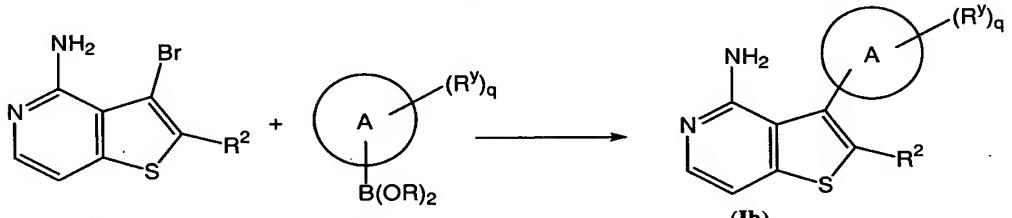


Compounds of formula (**Ia**) can be synthesized by the methods shown in Scheme 2. Compounds of formula (**6**) can be converted to compounds of formula (**8**) by transition metal-mediated cross-coupling with compounds of formula (**7**) (q is 1 or 2 and each R^x is independently selected from the group consisting of alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, heteroaryl, heterocyclyl, hydroxy, hydroxyalkyl, and NR^aR^b) in the presence of bis(pinacolato)diboron, potassium acetate, and a base. Examples of transition metal catalysts used in these couplings include, but are not limited to, $PdCl_2(dppf)$, $Pd(PPh_3)_4$, and $Pd(PPh_3)_2Cl_2$. Representative bases include sodium carbonate, potassium

carbonate, and cesium carbonate. The reaction is typically conducted at about 70 to about 90 °C for about 2 to about 24 hours.

Compounds of formula (**8**) can be converted to compounds of formula (**Ia**) (where L is selected from the group consisting of $NR^5C(O)(CH_2)_m$, NR^5SO_2, $(CH_2)_mN(R^5)C(O)N(R^6)(CH_2)_n$) by treatment with the appropriate acylating/sulfonylating reagent (i.e., a substituted acid chloride, sulfonyl chloride, or isocyanate) optionally in the presence of a base such as pyridine or triethylamine.

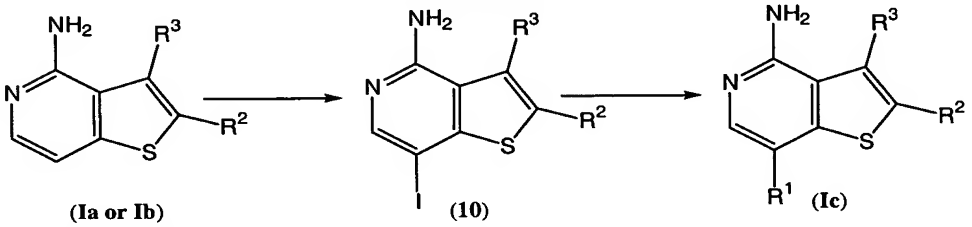
Scheme 3



(6) (9) (Ib)

As shown in Scheme 3, compounds of formula (**6**) can be reacted with compounds of formula (**9**) (where q is 1, 2, or 3 and each R^y is selected from the group consisting of alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, heteroaryl, heterocyclyl, hydroxy, hydroxyalkyl, LR^4, and NR^aR^b; provided that at least two of the three substituents are other than LR^4) in the presence of a transition metal catalyst and a base to provide compounds of formula (**Ia**). Examples of transition metal catalysts used in these couplings include, but are not limited to, $PdCl_2(dppf)$, $Pd(PPh_3)_4$, and $Pd(PPh_3)_2Cl_2$. Representative bases include sodium carbonate, potassium carbonate, and cesium carbonate.

Scheme 4



(Ia or Ib) (10) (Ic)

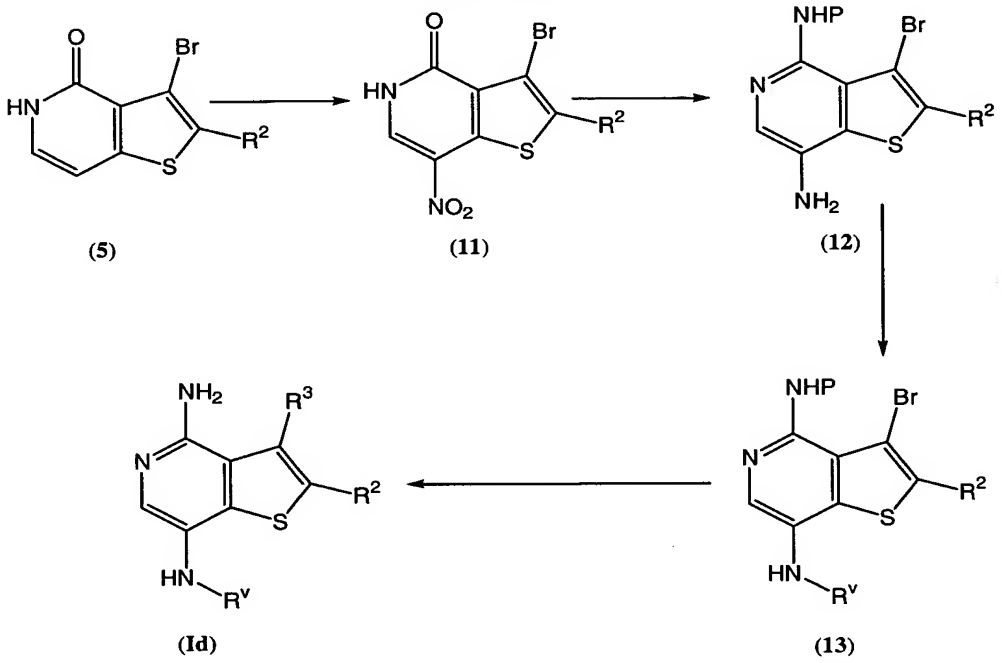
Compounds of formula (**Ic**) can be synthesized following the procedures shown in Scheme 4. Compounds of formula (**Ia**) or (**Ib**) can be reacted with N-iodosuccinimide at about 20 to about 35 °C for about 1 to about 4 hours to provide compounds of formula (**10**).

Compounds of formula (**Ic**) can be prepared by coupling compounds of formula (**10**) with an appropriately substituted organometallic coupling partner (for example, an organoborane or an organostannane) in the presence of a transition metal catalyst. Examples of transition metal catalysts used in these couplings include, but are not limited to, $PdCl_2(dppf)$, $Pd(PPh_3)_4$, and $Pd(PPh_3)_2Cl_2$. When an organoborane is used in the coupling, a

base is also required. Representative bases include sodium carbonate, potassium carbonate, and cesium carbonate.

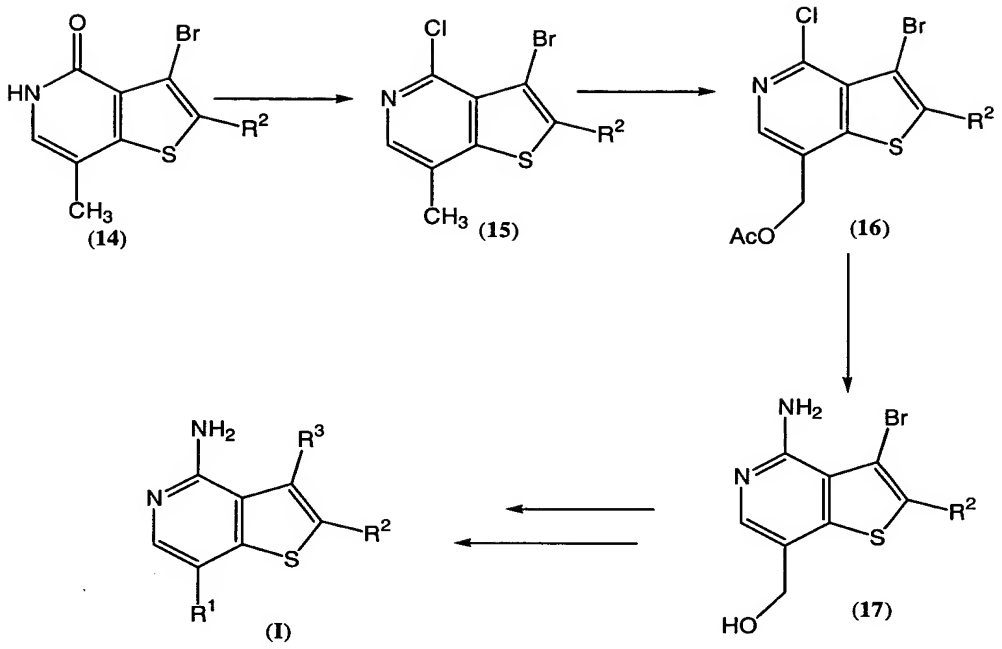
Compounds of formula (**Ic**) can be further functionalized at R^1 using methods known to those of ordinary skill in the art. For example, when R^1 contains an aldehyde (formed by coupling an alkenyl acetal with the compound of formula (**10**) and subsequent deprotection) reductive amination provides an alkenylamine. Similarly, when R^1 contains a primary amine, reaction with an aldehyde under reductive amination provides the secondary amine. In another example, when R^1 contains a carboxylic acid (prepared by hydrolysis of the corresponding ester) coupling with an amine provides an alkenylamide.

Scheme 5



The synthesis of compounds of formula (**Id**) is shown in Scheme 5. Compounds of formula (**5**) can be treated with nitric acid and sulfuric acid to provide compounds of formula (**11**). Conversion of the pyridone to the aminopyridine can be accomplished using the conditions described in Scheme 1. Protection of the amine followed by reduction of the nitro group using conditions known to those of ordinary skill in the art provides compounds of formula (**12**) where P is a nitrogen protecting group. The unprotected amine can be further functionalized by reacting with an appropriately substituted acyl halide, sulfonyl chloride, or isocyanate to provide compounds of formula (**13**) where R^v is the resulting functionality (i.e., alkylsulfonyl, alkylcarbonyl). Removal of the protecting group followed by coupling of the bromide as described in Scheme 2 or Scheme 3 provides compounds of formula (**Id**).

Scheme 6



As shown in Scheme 6, compounds of formula (**14**) (prepared according to the procedures described in Scheme 1 using 1-(4-bromo-2-thienyl)ethanone) can be converted to compounds of formula (**15**) by treatment with $POCl_3$ at about 108 °C for about 1 to about 4 hours. Reaction of compounds of formula (**15**) with benzoyl peroxide and N-bromosuccinimide followed by treatment with sodium acetate provides compounds of formula (**16**). This reaction is typically conducted at about 70 to about 100 °C for about 24 to about 48 hours.

Removal of the acetate group and displacement of the chloride can be accomplished by treating compounds of formula (**16**) with concentrated ammonium hydroxide at a temperature of about 120 to about 160 °C to provide compounds of formula (**17**). Coupling of the bromide using the conditions described in Schemes 2 or 3 and further functionalization of the hydroxymethyl group provides compounds of formula (**I**). An example of further functionalization is oxidation of the hydroxymethyl group to provide the aldehyde followed by reductive amination to provide an aminomethyl group.

The present invention will now be described in connection with certain preferred embodiments which are not intended to limit its scope. On the contrary, the present invention covers all alternatives, modifications, and equivalents as can be included within the scope of the claims. Thus, the following examples, which include preferred embodiments, will illustrate the preferred practice of the present invention, it being understood that the examples are for the purposes of illustration of certain preferred embodiments and are presented to provide what is believed to be the most useful and readily understood description of its procedures and conceptual aspects.

Compounds of the invention were named by ACD/ChemSketch version 5.0 (developed by Advanced Chemistry Development, Inc., Toronto, ON, Canada).

Example 1

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)-2-fluorophenyl]-N'-(3-methylphenyl)urea

Example 1A

3-bromothieno[3,2-c]pyridin-4(5H)-one

A suspension of (2E)-3-(4-bromo-2-thienyl)acrylic acid (commercially available, 50.2g, 0.215 mol) in dichloromethane (150 mL) was treated with DMF (2 drops) and $SOCl_2$ (23 mL, 0.315 mol), stirred at room temperature for 48 hours, heated to reflux for 2 hours, and concentrated. The residue was dissolved in dioxane (100 mL) and added to a vigorously stirred solution of NaN_3 (25g, 0.384 mol) in water (100 mL) and dioxane (100 mL) over 10 minutes. The resulting mixture was stirred at room temperature for 2.5 hours and extracted twice with 150 mL of ethyl acetate. The combined organics were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated. A solution of the residue in dichloromethane (150 mL) was added dropwise over 5 hours to boiling diphenyl ether (150 mL) in a 3-neck flask fitted with 2 air-cooled condensers. The mixture was stirred at reflux for an additional 1 hour, cooled to room temperature, and concentrated. The residue was suspended in diethyl ether (100 mL) and hexanes (200 mL), cooled, and filtered. The filter cake was washed with additional diethyl ether/hexanes and dried to provide 37.4g of the desired product. MS (ESI(+)) m/e 231 $(M+H)^+$.

Example 1B

3-bromothieno[3,2-c]pyridin-4-amine

A suspension of Example 1A (35.91g, 0.156 mol) in $POCl_3$ (80 mL) was heated to reflux for 2.5 hours, cooled to room temperature, poured onto 800g of ice, and extracted repeatedly with dichloromethane. The combined extracts were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel with 0 to 5% methanol/dichloromethane to provide 29.3g of 3-bromo-4-chlorothieno[3,2-c]pyridine (mp 158-159 °C), which was diluted with dioxane (500 mL) and concentrated aqueous NH_3 (500 mL), heated to 150 °C under pressure (260 psi) for 20 hours, and concentrated. The residue was triturated from MTBE then from methanol to provide 20.29g of the desired product. m.p. 153-155 °C.

Example 1C

3-(4-amino-3-fluorophenyl)thieno[3,2-c]pyridin-4-amine

A solution of 4-bromo-2-fluoroaniline (1.83g, 9.6 mmol), bis(pinacolato)diboron (2.65g, 10.4 mmol) and potassium acetate (2.56g, 26.1 mmol) in DMF (50 mL) was purged with nitrogen, treated with $PdCl_2$(dppf) (0.355g, 0.05 mmol), heated to 80 °C for 2.5 hours, cooled to room temperature, and treated with a solution of Na_2CO_3 (4.61g, 43.5 mmol) in water (20 mL), Example 1B (2.02g, 8.8 mmol), and additional $PdCl_2$(dppf) (0.355g, 0.05 mmol). The mixture was heated to 80 °C overnight, cooled to room temperature, poured into water, and extracted with ethyl acetate. The organic extract was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel with 50 to 60% ethyl acetate/hexanes (0.5% triethylamine added) to provide 1.5g of the desired product. MS (ESI(+)) m/e 260 $(M+H)^+$.

Example 1D

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)-2-fluorophenyl]-N'-(3-methylphenyl)urea

A solution of Example 1C (125mg, 0.48 mmol) in dichloromethane (1mL) was treated with 1-isocyanato-3-methylbenzene (0.065 mL, 0.5 mmol), stirred overnight at room temperature, and filtered. The filter cake was purified by preparative HPLC on a Waters Symmetry C8 column (25mm x 100mm, 7μm particle size) using a solvent gradient of 10% to 100% acetonitrile/10mM aqueous ammonium acetate over 8 minutes (10 minute run time) at a flow rate of 40mL/minute to provide 74 mg of the desired product. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30 (s, 3H), 5.48 (s, 2H), 6.83 (d, J=7.8 Hz, 1H), 7.18 (t, J=7.6 Hz, 1H), 7.22-7.29 (m, 2H), 7.28 (d, J=5.8 Hz, 1H), 7.32 (s, 1H), 7.38 (dd, J=12.0, 1.9 Hz, 1H), 7.50 (s, 1H), 7.84 (d, J=5.8 Hz, 1H), 8.31 (t, J=8.5 Hz, 1H), 8.70 (d, J=2.4 Hz, 1H), 9.06 (s, 1H); MS (ESI(+)) m/e 393.0 $(M+H)^+$.

Example 2

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)-2-fluorophenyl]-N'-(3-chlorophenyl)urea

The desired product was prepared by substituting 1-isocyanato-3-chlorobenzene for 1-isocyanato-3-methylbenzene in Example 1. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.44 (s, 2H), 7.06 (ddd, J=7.8, 2.0, 1.4 Hz, 1H), 7.24-7.25 (m, J=1.7 Hz, 1H), 7.27 (d, J=5.4 Hz, 1H), 7.26-7.27 (m, 1H), 7.34 (t, J=8.1 Hz, 1H), 7.39 (dd, J=11.9, 2.0 Hz, 1H), 7.50 (s, 1H), 7.75 (t, J=2.0 Hz, 1H), 7.84 (d, J=5.8 Hz, 1H), 8.27 (t, J=8.5 Hz, 1H), 8.78 (d, J=2.4 Hz, 1H), 9.32 (s, 1H); MS (ESI(+)) m/e 413.0, 415.1 $(M+H)^+$.

Example 3

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)-2-fluorophenyl]-N'-[3-(trifluoromethyl)phenyl]urea

The desired product was prepared by substituting 1-isocyanato-3-trifluoromethylbenzene for 1-isocyanato-3-methylbenzene in Example 1. ^{1}H NMR (300

MHz, DMSO-d_6) d 5.45 (s, 2H), 7.26 (dd, J=8.1, 1.7 Hz, 1H), 7.28 (d, J=5.8 Hz, 1H), 7.34-7.37 (m, 1H), 7.40 (dd, J=12.0, 1.9 Hz, 1H), 7.51 (s, 1H), 7.54-7.57 (m, 2H), 7.84 (d, J=5.4 Hz, 1H), 8.06 (s, 1H), 8.27 (t, J=8.5 Hz, 1H), 8.81 (d, J=2.4 Hz, 1H), 9.47 (s, 1H); MS (ESI(+)) m/e 447.0 $(M+H)^+$.

Example 4

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)-2-fluorophenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea

The desired product was prepared by substituting 1-fluoro-2-isocyanato-4-(trifluoromethyl)benzene for 1-isocyanato-3-methylbenzene in Example 1. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.43 (s, 2H), 7.26 (dd, J=9.0, 2.2 Hz, 1H), 7.28 (d, J=5.4 Hz, 1H), 7.41 (dd, J=12.0, 1.9 Hz, 1H), 7.40-7.45 (m, 1H), 7.51 (s, 1H), 7.53 (dd, J=11.2, 8.5 Hz, 1H), 7.85 (d, J=5.8 Hz, 1H), 8.32 (t, J=8.5 Hz, 1H), 8.66 (dd, J=7.3, 2.2 Hz, 1H), 9.33 (d, J=2.4 Hz, 1H), 9.45 (d, J=2.7 Hz, 1H); MS (ESI(+)) m/e 465.0 $(M+H)^+$.

Example 5

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)-2-fluorophenyl]-N'-(3-bromophenyl)urea

The desired product was prepared by substituting 1-bromo-3-isocyanatobenzene for 1-isocyanato-3-methylbenzene in Example 1. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.44 (s, 2H), 7.19 (dt, J=7.1, 1.9 Hz, 1H), 7.24-7.33 (m, 4H), 7.39 (dd, J=11.9, 2.0 Hz, 1H), 7.50 (s, 1H), 7.84 (d, J=5.8 Hz, 1H), 7.89-7.91 (m, 1H), 8.27 (t, J=8.5 Hz, 1H), 8.77 (d, J=2.7 Hz, 1H), 9.31 (s, 1H); MS (ESI(+)) m/e 457.0, 458.8 $(M+H)^+$.

Example 6

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)-3-fluorophenyl]-N'-(3-methylphenyl)urea

Example 6A

3-(4-amino-2-fluorophenyl)thieno[3,2-c]pyridin-4-amine

The desired product was prepared by substituting 4-bromo-3-fluoroaniline for 4-bromo-2-fluoroaniline in Example 1C. MS (ESI(+)) m/e 260.0 $(M+H)^+$.

Example 6B

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)-3-fluorophenyl]-N'-(3-methylphenyl)urea

The desired product was prepared by substituting Example 6A for Example 1C in Example 1D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 5.34 (s, 2H), 6.82 (d, J=7.1 Hz, 1H), 7.18 (t, J=7.6 Hz, 1H), 7.24-7.28 (m, 3H), 7.32 (s, 1H), 7.37 (t, J=8.5 Hz, 1H), 7.53 (s, 1H), 7.65 (dd, J=12.2, 2.0 Hz, 1H), 7.83 (d, J=5.4 Hz, 1H), 8.73 (s, 1H), 9.06 (s, 1H); MS

(ESI(+)) m/e 393.0 $(M+H)^+$.

Example 7

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)-3-fluorophenyl]-N'-[3-(trifluoromethyl)phenyl]urea

The desired product was prepared by substituting Example 6A and 1-isocyanato-3-(trifluoromethyl)benzene for Example 1C and 1-isocyanato-3-methylbenzene, respectively, in Example 1D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.34 (s, 2H), 7.28 (d, J=5.8 Hz, 1H), 7.30-7.42 (m, 3H), 7.51-7.57 (m, 2H), 7.61-7.68 (m, 2H), 7.83 (d, J=5.8 Hz, 1H), 8.02 (s, 1H), 9.21 (s, 1H), 9.22 (s, 1H); MS (ESI(+)) m/e 447.0 $(M+H)^+$.

Example 8

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)-3-fluorophenyl]-N'-(3-chlorophenyl)urea

The desired product was prepared by substituting Example 6A and 1-chloro-3-isocyanatobenzene for Example 1C and 1-isocyanato-3-methylbenzene, respectively, in Example 1D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.34 (s, 2H), 7.05 (ddd, J=6.2, 2.4, 2.2 Hz, 1H), 7.27 (d, J=5.4 Hz, 1H), 7.28-7.32 (m, 3H), 7.39 (t, J=8.3 Hz, 1H), 7.54 (s, 1H), 7.64 (dd, J=12.5, 2.0 Hz, 1H), 7.72-7.73 (m, 1H), 7.83 (d, J=5.4 Hz, 1H), 9.04 (s, 1H), 9.17 (s, 1H); MS (ESI(+)) m/e 413.0, 414.9 $(M+H)^+$.

Example 9

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)-3-chlorophenyl]-N'-(3-methylphenyl)urea

Example 9A

3-(4-amino-2-chlorophenyl)thieno[3,2-c]pyridin-4-amine

The desired product was prepared by substituting 4-bromo-3-chloroaniline for 4-bromo-2-fluoroaniline in Example 1C. MS (ESI(+)) m/e 275.9, 278.1 $(M+H)^+$.

Example 9B

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)-3-chlorophenyl]-N'-(3-methylphenyl)urea

The desired product was prepared by substituting Example 9A for Example 1C in Example 1D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 5.22 (s, 2H), 6.82 (d, J=7.1 Hz, 1H), 7.18 (t, J=7.8 Hz, 1H), 7.24-7.26 (m, 1H), 7.26 (d, J=5.4 Hz, 1H), 7.33 (s, 1H), 7.41 (app. s, 2H), 7.48 (s, 1H), 7.82 (d, J=5.8 Hz, 1H), 7.91 (s, 1H), 8.75 (s, 1H), 9.04 (s, 1H); MS (ESI(+)) m/e 409.0, 411.1 $(M+H)^+$.

Example 10

3-(4-phenoxyphenyl)-7-(4-pyridinyl)thieno[3,2-c]pyridin-4-amine

Example 10A

3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-4-amine

A mixture of Example 1B (1.5g, 6.5 mmol), 4-phenoxyphenylboronic acid (1.53g, 7.1 mmol) and Na_2CO_3 (1.81g, 17.1 mmol) in toluene (26 mL), ethanol (5 mL), and water (10 mL) was purged with nitrogen for 45 minutes, then treated with $Pd(PPh_3)_4$ (0.382g, 0.33 mmol) and heated to 90 °C overnight. The reaction was cooled to room temperature and partitioned between water and ethyl acetate. The aqueous phase was extracted with ethyl acetate twice and the combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel with 40% ethyl acetate/hexanes to provide 1.69g (82% yield) of the desired product. MS (ESI(+)) m/e 318.9 $(M+H)^+$.

Example 10B

7-iodo-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-4-amine

A solution of Example 10A (1.69g, 5.3 mmol) in DMF (20 mL) was treated with NIS (1.26g, 5.6 mmol), stirred at room temperature for 3 hours, poured into water, and filtered. The filter cake was purified by flash column chromatography on silica gel with 15% ethyl acetate/hexanes to provide 1.64g (70% yield) of the desired product. MS (ESI(+)) m/e 444.8 $(M+H)^+$.

Example 10C

3-(4-phenoxyphenyl)-7-(4-pyridinyl)thieno[3,2-c]pyridin-4-amine

The desired product was prepared by substituting Example 10B, 4-pyridylboronic acid, and $PdCl_2(dppf)$ for Example 1B, 4-phenoxyphenylboronic acid, and $Pd(PPh_3)_4$ respectively, in Example 10A. ^1H NMR (300 MHz, DMSO-d_6) δ 5.74 (s, 2H), 7.12-7.16 (m, 4H), 7.21 (t, *J*=7.5 Hz, 1H), 7.45 (dd, *J*=8.7, 7.3 Hz, 2H), 7.50 (d, *J*=8.5 Hz, 2H), 7.58 (s, 1H), 7.72 (d, *J*=6.1 Hz, 2H), 8.09 (s, 1H), 8.68 (d, *J*=6.1 Hz, 2H); MS (ESI(+)) m/e 396.0 $(M+H)^+$.

Example 11

4-{(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-2-propenoyl}-2-piperazinone

Example 11A

tert-butyl (2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]acrylate

A mixture of Example 10B (0.417g, 0.94 mmol), tert-butyl acrylate (0.26 mL, 1.74

mol) and triethylamine (0.7 mL, 5 mmol) in DMF (3 mL) was degassed with nitrogen for 45 minutes, treated with $PdCl_2(o\text{-}tol_3P)_2$ (0.032g, 0.046 mmol), and heated to 80 °C overnight. The resulting mixture was cooled to room temperature, then partitioned between water and ethyl acetate. The organic extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel with 30% ethyl acetate/hexanes to provide 0.25g (61% yield) of the desired product. MS (ESI(+)) m/e 445 $(M+H)^+$.

Example 11B

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]acrylic acid

A solution of Example 11A (0.25g, 0.57 mmol) in TFA (5 mL) was stirred at room temperature for 14 hours then concentrated under a stream of nitrogen to provide the desired product. MS (ESI(+)) m/e 388.9 $(M+H)^+$.

Example 11C

4-{(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-2-propenoyl}-2-piperazinone

A mixture of Example 11B (0.09g, 0.23 mmol), 2-piperazinone (0.069g, 0.69 mmol), HOBT (0.095g, 0.7 mmol), N-methylmorpholine (0.22 mL, 0.92 mmol), and EDCI (0.136g, 0.71 mmol) in DMF (1 mL) was stirred at room temperature overnight, treated with water (20 mL), and filtered. The filter cake was dried to provide 110mg of the desired product. ^1H NMR (300 MHz, DMSO-d_6) δ 3.20-3.36 (br m, 2H), 3.71-3.91 (br m, 2H), 4.03-4.35 (m, 2H), 5.94 (br s, 2H), 6.92-7.15 (br m, 1H), 7.11-7.16 (m, 4H), 7.21 (t, J=7.3 Hz, 1H), 7.42-7.52 (m, 4H), 7.63 (s, 1H), 7.71 (d, J=14.9 Hz, 1H), 8.13 (br s, 1H), 8.33 (s, 1H); MS (ESI(-)) m/e 469.3 $(M-H)^-$.

Example 12

tert-butyl (2E)-3-(4-amino-3-phenylthieno[3,2-c]pyridin-7-yl)acrylate

Example 12A

7-iodo-3-phenylthieno[3,2-c]pyridin-4-amine

The desired product was prepared by substituting phenylboronic acid for 4-phenoxyphenylboronic acid in Example 10A and 10B.

Example 12B

tert-butyl (2E)-3-(4-amino-3-phenylthieno[3,2-c]pyridin-7-yl)acrylate

The desired product was prepared by substituting Example 12A for Example 10B in

Example 11A. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.51 (m, 9H), 5.95 (br s, 1H), 6.33 (d, J=15.9 Hz, 1H), 7.53 (m, 5H), 7.64 (s, 1H), 7.72 (d, J=16.3 Hz, 1H), 8.24 (s, 1H); MS (ESI(+)) m/e 353 $(M+H)^+$.

Example 13

(2E)-3-(4-amino-3-phenylthieno[3,2-c]pyridin-7-yl)acrylic acid

The desired product was prepared as the trifluoroacetate salt by substituting Example 12B for Example 11A in Example 11B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.52 (d, J=16.3 Hz, 1H), 6.6-6.8 (br s, 2H), 7.55 (m, 5H), 7.76 (d, J=16.3 Hz, 1H), 7.86 (s, 1H), 8.34 (s, 1H); MS (ESI(+)) m/e 297 $(M+H)^+$.

Example 14

(2E)-3-(4-amino-3-phenylthieno[3,2-c]pyridin-7-yl)-N-methylacrylamide

A mixture of Example 13 (0.1g, 0.34 mmol), methylamine hydrochloride (0.115g, 1.69 mmol), HOBT (0.137g, 1.01 mmol), N-methylmorpholine (0.25 mL, 2.36 mmol), and EDCI (0.199g, 1.01 mmol) in DMF (5 mL) was stirred at room temperature for 2 hours, diluted with water (20 mL), and extracted with ethyl acetate (2 x 20 mL). The combined extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated to provide 89 mg of the desired product. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.73 (d, J=4.8 Hz, 3H), 5.75-5.85 (br s, 2H), 6.58 (d, J=15.9 Hz, 1H), 7.53 (m, 5H), 7.58 (d, J=15.9 Hz, 1H), 7.67 (s, 1H), 8.14 (m, 2H); MS (ESI(+)) m/e 310 $(M+H)^+$.

Example 15

3-(4-amino-3-phenylthieno[3,2-c]pyridin-7-yl)-N-methylpropanamide

A mixture of Example 14 (30mg, 0.1mmol) and 10% Pd on carbon (30 mg) in 1:1 methanol/DMF (4 mL) was stirred under an atmosphere of hydrogen overnight. The suspension was filtered through diatomaceous earth (Celite®). The pad was washed with methanol and the filtrate was concentrated to half its original volume. The residue was diluted with diethyl ether and filtered. The filter cake was dried to provide 26 mg of the desired product. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.47 (m, 2H), 2.58 (d, J=4.6 Hz, 2H), 2.91 (t, J=7.9 Hz, 2H), 5.21 (s, 1H), 7.50 (m, 6H), 7.66 (s, 1H), 7.81 (m, J=4.3 Hz, 1H); MS (ESI(+)) m/e 312 $(M+H)^+$.

Example 16

4-[(2E)-3-(4-amino-3-phenylthieno[3,2-c]pyridin-7-yl)-2-propenoyl]-2-piperazinone

The desired product was prepared by substituting Example 13 for Example 11B in Example 11C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.82 (br m, 2H), 4.20 (br m, 2H), 5.86 (br

s, 2H), 7.03 (br m, 1H), 7.53 (m, 5H), 7.64 (s, 1H), 7.71 (d, J=14.9 Hz, 1H), 8.14 (s, 1H), 8.33 (s, 1H); MS (ESI(+)) m/e 379 $(M+H)^+$.

Example 17

tert-butyl (2E)-3-{3-[4-(acetylamino)phenyl]-4-aminothieno[3,2-c]pyridin-7-yl}acrylate

Example 17A

3-(4-aminophenyl)thieno[3,2-c]pyridin-4-amine

The desired product was prepared by substituting 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline for 4-phenoxyphenylboronic acid in Example 10A. MS (ESI(+)) m/e 242 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.35 (s, 2H), 5.48 (s, 2H), 6.66 (d, J=8.14 Hz, 2H), 7.08 (d, J=8.14 Hz, 2H), 7.20 (d, J=5.42 Hz, 1H), 7.27 (s, 1H), 7.78 (d, J=5.76 Hz, 1H).

Example 17B

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]acetamide

A -30 °C solution of Example 17A (0.1g, 0.41 mmol) and N-methylmorpholine (0.03 mL, 0.41 mmol) in THF (5 mL) was treated dropwise with acetyl chloride (0.03 mL, 0.41 mmol), stirred for 1 hour, warmed to 0 °C over 1 hour, quenched with water, and extracted twice with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated to provide 111 mg of the desired product. R_f = 0.24 (5% methanol/dichloromethane).

Example 17C

N-[4-(4-amino-7-iodothieno[3,2-c]pyridin-3-yl)phenyl]acetamide

The desired product was prepared by substituting Example 17B for Example 10A in Example 10B.

Example 17D

tert-butyl (2E)-3-{3-[4-(acetylamino)phenyl]-4-aminothieno[3,2-c]pyridin-7-yl}acrylate

The desired product was prepared by substituting Example 17C for Example 10B in Example 11A. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.51 (m, 9H), 2.09 (m, 3H), 5.98 (s, 2H), 6.31 (d, J=15.9 Hz, 1H), 7.41 (d, J=8.5 Hz, 2H), 7.59 (s, 1H), 7.72 (m, 3H), 8.23 (s, 1H), 10.14 (s, 1H); MS (ESI(+)) m/e 410 $(M+H)^+$.

Example 18

(2E)-3-{3-[4-(acetylamino)phenyl]-4-aminothieno[3,2-c]pyridin-7-yl}acrylic acid

The desired product was prepared as the trifluoroacetate salt by substituting Example 17D for Example 11A in Example 11B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.10 (m, 3H), 6.51 (d, J=16.3 Hz, 1H), 6.74 (br s, 2H), 7.44 (d, J=8.5 Hz, 2H), 7.76 (dd, J=16.6, 7.8 Hz, 4H), 8.33 (s, 1H), 10.18 (s, 1H); MS (ESI(+)) m/e 354 $(M+H)^+$.

Example 19

(2E)-3-{3-[4-(acetylamino)phenyl]-4-aminothieno[3,2-c]pyridin-7-yl}-N-methylacrylamide

The desired product was prepared by substituting Example 18 for Example 13 in Example 14. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.09 (m, 3H), 2.73 (m, 3H), 5.82 (s, 2H), 6.57 (d, J=15.9 Hz, 1H), 7.41 (d, J=8.5 Hz, 2H), 7.59 (m, 2H), 7.73 (d, J=8.5 Hz, 2H), 8.14 (m, 2H), 10.14 (s, 1H); MS (ESI(+)) m/e 367 $(M+H)^+$.

Example 20

N-(4-{4-amino-7-[(1E)-3-oxo-3-(3-oxo-1-piperazinyl)-1-propenyl]thieno[3,2-c]pyridin-3-yl}phenyl)acetamide

The desired product was prepared by substituting Example 18 for Example 11B in Example 11C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.09 (m, 3H), 3.81 (br m, 2H), 4.19 (br m, 2H), 5.89 (br s, 2H), 7.02 (br m, 1H), 7.41 (d, J=8.5 Hz, 2H), 7.59 (s, 1H), 7.72 (m, 3H), 8.14 (br s, 1H), 8.32 (s, 1H), 10.14 (s, 1H); MS (ESI(+)) m/e 436 $(M+H)^+$.

Example 21

(2E)-3-[4-amino-3-(4-chlorophenyl)thieno[3,2-c]pyridin-7-yl]-N-methylacrylamide

Example 21A

3-bromo-7-iodothieno[3,2-c]pyridin-4-amine

The desired product was prepared by substituting Example 1B for Example 10A in Example 10B.

Example 21B

(2E)-3-(4-amino-3-bromothieno[3,2-c]pyridin-7-yl)-N-methylacrylamide

The desired product was prepared by substituting Example 21A for Example 10B and methylamine for piperazin-2-one in Examples 11A-C. MS (ESI(+)) m/e 311.6,313.6 $(M+H)^+$.

Example 21C

(2E)-3-[4-amino-3-(4-chlorophenyl)thieno[3,2-c]pyridin-7-yl]-N-methylacrylamide

A mixture of Example 21B (150mg, 0.48 mmol), 4-chlorophenylboronic acid (75mg,

0.48 mmol), $PdCl_2(PPh_3)_2$ (3mg) and Cs_2CO_3 (188 mg) in DME/water/ethanol (70:30:20 mixture, 2 mL) was heated in a sealed vial to 160 °C for 7.5 minutes with stirring in a Smith Synthesizer microwave oven (at 300W). The reaction was partinioned between water and dichloromethane and the organic layer was concentrated. The residue collected was purified by preparative HPLC on a Waters Symmetry C8 column (25mm x 100mm, 7μm particle size) using a gradient of 10% to 100% acetonitrile:5 mM aqueous ammonium acetate over 8 minutes (10 minute run time) at a flow rate of 40mL/min to provide 59 mg (36% yield) of the desired product. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.73 (d, *J*=4.7 Hz, 3H), 5.81 (s, 2H), 6.58 (d, *J*=15.9 Hz, 1H), 7.51 (d, *J*=8.5 Hz, 2H), 7.58 (d, *J*=15.9 Hz, 1H), 7.60 (d, *J*=8.5 Hz, 2H), 7.70 (s, 1H), 8.13 (s, 1H), 8.16 (q, *J*=4.7 Hz, 1H), MS (ESI(-)) m/e 341.8 $(M-H)^-$.

Examples 22-35 were prepared by substituting the appropriate boronic acid (X) for 4-chloro-phenylboronic acid in Example 21C.

Example 22

(2E)-3-{4-amino-3-[4-(trifluoromethoxy)phenyl]thieno[3,2-c]pyridin-7-yl}-N-methylacrylamide

X = 4-trifluoromethoxyphenylboronic acid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.73 (d, *J*=4.7 Hz, 3H), 5.83 (s, 2H), 6.59 (d, *J*=15.9 Hz, 1H), 7.52 (dd, *J*=8.8, 1.0 Hz, 2H), 7.58 (d, *J*=15.9 Hz, 1H), 7.63 (d, *J*=8.8 Hz, 2H), 7.75 (s, 1H), 8.14 (s, 1H), 8.16 (q, *J*=4.7 Hz, 1H); MS (ESI(+)) m/e 393.9 $(M+H)^+$.

Example 23

(2E)-3-[4-amino-3-(1,3-benzodioxol-5-yl)thieno[3,2-c]pyridin-7-yl]-N-methylacrylamide

X = 1,3-benzodioxol-5-ylboronic acid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.73 (d, *J*=4.7 Hz, 3H), 5.89 (s, 2H), 6.12 (s, 2H), 6.56 (d, *J*=15.6 Hz, 1H), 6.93 (dd, *J*=7.8, 1.7 Hz, 1H), 7.05 (d, *J*=1.7 Hz, 1H), 7.06 (d, *J*=7.8 Hz, 1H), 7.57 (d, *J*=15.6 Hz, 1H), 7.61 (s, 1H), 8.11 (s, 1H), 8.14 (q, *J*=4.7 Hz, 1H); MS (ESI(+)) m/e 353.9 $(M+H)^+$.

Example 24

(2E)-3-[4-amino-3-(4-methylphenyl)thieno[3,2-c]pyridin-7-yl]-N-methylacrylamide

X = 4-methylphenylboronic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.49 (s, 3H), 2.82 (d, *J*=4.6 Hz, 3H), 5.88 (s, 2H), 6.66 (d, *J*=16.0 Hz, 1H), 7.44 (m, 4H), 7.66 (d, *J*=16.0 Hz, 1H), 7.69 (s, 1H), 8.20 (s, 1H), 8.22 (q, *J*=4.6 Hz, 1H); MS (ESI(+)) m/e 324.0 $(M+H)^+$.

Example 25

(2E)-3-[4-amino-3-(4-fluorophenyl)thieno[3,2-c]pyridin-7-yl]-N-methylacrylamide

X = 4-fluorophenylboronic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.73 (d, *J*=4.6 Hz, 3H), 5.78 (s, 2H), 6.58 (d, *J*=16.0 Hz, 1H), 7.37 (t, *J*=8.8 Hz, 2H), 7.54 (dd, *J*=8.8, 5.5 Hz, 2H), 7.58 (d, *J*=16.0 Hz, 1H), 7.67 (s, 1H), 8.13 (s, 1H), 8.14 (q, *J*=4.6 Hz, 1H); MS (ESI(+)) m/e 327.9 $(M+H)^+$.

Example 26

(2E)-3-[4-amino-3-(4-methoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-methylacrylamide

X = 4-methoxyphenylboronic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.50 (d, *J*=4.6 Hz, 3H), 3.60 (s, 3H), 5.58 (s, 2H), 6.34 (d, *J*=16.0 Hz, 1H), 6.86 (d, *J*=8.8 Hz, 2H), 7.17 (d, *J*=8.8 Hz, 2H), 7.34 (d, *J*=16.0 Hz, 1H), 7.35 (s, 1H), 7.87 (s, 1H), 7.90 (q, *J*=4.6 Hz, 1H); MS (ESI(+)) m/e 339.9 $(M+H)^+$.

Example 27

(2E)-3-{4-amino-3-[4-(trifluoromethyl)phenyl]thieno[3,2-c]pyridin-7-yl}-N-methylacrylamide

X = 4-(trifluoromethyl)phenylboronic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.50 (d, *J*=4.6 Hz, 3H), 5.56 (s, 2H), 6.35 (d, *J*=16.0 Hz, 1H), 7.35 (d, *J*=16.0 Hz, 1H), 7.49 (d, *J*=8.0 Hz, 2H), 7.54 (s, 1H), 7.65 (d, *J*=8.0 Hz, 2H), 7.91 (q, *J*=4.6 Hz, 1H), 7.92 (s, 1H); MS (ESI(+)) m/e 377.9 $(M+H)^+$.

Example 28

(2E)-3-{4-amino-3-[4-(benzyloxy)phenyl]thieno[3,2-c]pyridin-7-yl}-N-methylacrylamide

X = 4-(benzyloxy)phenylboronic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.50 (d, *J*=4.6 Hz, 3H), 4.95 (s, 2H), 5.59 (s, 2H), 6.34 (d, *J*=16.0 Hz, 1H), 6.94 (d, *J*=8.6 Hz, 2H), 7.12 (t, *J*=7.2 Hz, 1H), 7.16-7.20 (m, 4H), 7.26 (d, *J*=7.0 Hz, 2H), 7.34 (d, *J*=16.0 Hz, 1H), 7.36 (s, 1H), 7.87 (s, 1H), 7.90 (q, *J*=4.6 Hz, 1H); MS (ESI(+)) m/e 416.0 $(M+H)^+$.

Example 29

(2E)-3-[4-amino-3-(1H-indol-5-yl)thieno[3,2-c]pyridin-7-yl]-N-methylacrylamide

X = 1H-indol-5-ylboronic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.80 (d, *J*=4.7 Hz, 3H), 5.86 (s, 2H), 6.58 (m, 1H), 6.65 (d, *J*=15.7 Hz, 1H), 7.21 (dd, *J*=8.3, 1.8 Hz, 1H), 7.53 (app t, *J*=2.5 Hz, 1H), 7.61 (d, *J*=8.3 Hz, 1H), 7.64 (s, 1H), 7.65 (d, *J*=15.7 Hz, 1H), 7.70 (d, *J*=1.8 Hz, 1H), 8.16 (s, 1H), 8.20 (q, *J*=4.7 Hz, 1H), 11.39 (s, 1H); MS (ESI(+)) m/e 348.9 $(M+H)^+$.

Example 30

(2E)-3-[4-amino-3-(3-aminophenyl)thieno[3,2-c]pyridin-7-yl]-N-methylacrylamide

X = 3-aminophenylboronic acid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.73 (d, *J*=4.4 Hz, 3H), 5.37 (s, 2H), 5.98 (s, 2H), 6.52-6.56 (m, 1H), 6.56 (d, *J*=15.9 Hz, 1H), 6.60 (t, *J*=2.0 Hz, 1H), 6.68 (ddd, *J*=8.1, 2.0, 0.7 Hz, 1H), 7.16 (t, *J*=7.6 Hz, 1H), 7.57 (d, *J*=15.9 Hz, 1H), 7.57 (s, 1H), 8.09 (s, 1H), 8.14 (q, *J*=4.4 Hz, 1H); MS (ESI(+)) m/e 325.0 $(M+H)^+$.

Example 31

(2E)-3-[4-amino-3-(4-bromophenyl)thieno[3,2-c]pyridin-7-yl]-N-methylacrylamide

X = 4-bromophenylboronic acid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.73 (d, *J*=4.7 Hz, 3H), 5.82 (s, 2H), 6.58 (d, *J*=15.9 Hz, 1H), 7.45 (d, *J*=8.5 Hz, 2H), 7.58 (d, *J*=15.9 Hz, 1H), 7.71 (s, 1H), 7.73 (d, *J*=8.5 Hz, 2H), 8.13 (s, 1H), 8.15 (q, *J*=4.7 Hz, 1H); MS (ESI(+)) m/e 387.8, 389.8 $(M+H)^+$.

Example 32

(2E)-3-[4-amino-3-(1,1'-biphenyl-4-yl)thieno[3,2-c]pyridin-7-yl]-N-methylacrylamide

X = 1,1'-biphenyl-4-ylboronic acid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.74 (d, *J*=4.7 Hz, 3H), 5.88 (s, 2H), 6.59 (d, *J*=15.9 Hz, 1H), 7.41 (t, *J*=7.3 Hz, 1H), 7.47-7.62 (m, 2H), 7.59 (d, *J*=15.6 Hz, 1H), 7.59 (d, *J*=8.5 Hz, 2H), 7.72 (s, 1H), 7.73-7.87 (m, 4H), 8.14 (s, 1H), 8.16 (q, *J*=4.7 Hz, 1H); MS (ESI(+)) m/e 386.0 $(M+H)^+$.

Example 33

(2E)-3-[4-amino-3-(4-cyanophenyl)thieno[3,2-c]pyridin-7-yl]-N-methylacrylamide

X = 4-cyanophenylboronic acid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.73 (d, *J*=4.4 Hz, 3H), 5.86 (s, 2H), 6.58 (d, *J*=15.9 Hz, 1H), 7.59 (d, *J*=15.9 Hz, 1H), 7.69 (d, *J*=8.5 Hz, 2H), 7.80 (s, 1H), 7.99 (d, *J*=8.5 Hz, 2H), 8.15 (q, *J*=4.4 Hz, 1H), 8.16 (s, 1H); MS (ESI(+)) m/e 335.0 $(M+H)^+$.

Example 34

(2E)-3-[4-amino-3-(3-methylphenyl)thieno[3,2-c]pyridin-7-yl]-N-methylacrylamide

X = 3-methylphenylboronic acid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.39 (s, 3H), 2.73 (d, *J*=4.7 Hz, 3H), 5.80 (s, 2H), 6.58 (d, *J*=15.9 Hz, 1H), 7.26-7.35 (m, 3H), 7.43 (t, *J*=7.5 Hz, 1H), 7.58 (d, *J*=15.9 Hz, 1H), 7.64 (s, 1H), 8.12 (s, 1H), 8.15 (q, *J*=4.7 Hz, 1H); MS (ESI(+)) m/e 324.0 $(M+H)^+$.

Example 35

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-methylacrylamide

X = 4-phenoxyphenylboronic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.73 (d, *J*=4.6 Hz, 3H), 5.97 (s, 2H), 6.60 (d, *J*=15.7 Hz, 1H), 7.12-7.15 (m, 4H), 7.21 (t, *J*=7.4 Hz, 1H),

7.45 (dd, J=8.3, 7.4 Hz, 2H), 7.50 (d, J=8.6 Hz, 2H), 7.58 (d, J=15.7 Hz, 1H), 7.69 (s, 1H), 8.14 (s, 1H), 8.16 (q, J=4.6 Hz, 1H); MS (ESI(+)) m/e 402.0 $(M+H)^+$.

Example 36

(2E)-3-[4-amino-3-(3-phenoxy-1-propynyl)thieno[3,2-c]pyridin-7-yl]-N-methylacrylamide

A mixture of Example 21A (150mg, 0.48 mmol), (2-propynyloxy)benzene (0.13 mL, 0.96 mmol), $PdCl_2(PPh_3)_2$ (17mg, 0.024 mmol), PPh_3 (15mg, 0.057 mmol), CuI (3 mg), and Et_3N (1 mL, 7.2 mmol) in DME/water/ethanol (70:30:20 mixture, 2 mL) was heated in a sealed vial to125 °C for 25 minutes with stirring in a Smith Synthesizer microwave oven (at 300W). The reaction mixture was concentrated and the residue was purified by HPLC using the conditions described in Example 21C to provide 47 mg (27% yield) of the desired product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.71 (d, J=4.6 Hz, 3H), 5.18 (s, 2H), 6.50 (d, J=16.0 Hz, 1H), 6.91 (s, 2H), 7.00 (t, J=7.4 Hz, 1H), 7.08 (dd, J=8.8, 0.9 Hz, 2H), 7.35 (dd, J=8.8, 7.4 Hz, 2H), 7.52 (d, J=16.0 Hz, 1H), 8.10-8.13 (m, 2H), 8.14 (s, 1H); MS (ESI(+)) m/e 364.0 $(M+H)^+$.

Examples 37-65 were prepared by substituting Example 17A and the appropriate isocyanide (X) for Example 1C and 1-isocyanato-3-methylbenzene, respectively, in Example 1D. The crude product was purified either by trituration from dichloromethane by flash column chromatography on silica gel.

Example 37

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]-N'-(3-methylphenyl)urea

X = 1-isocyanato-3-methylbenzene. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 5.44 (s, 2H), 6.81 (d, J=7.12 Hz, 1H), 7.17 (t, J=7.80 Hz, 1H), 7.26 (d, J=5.76 Hz, 2H), 7.34 (d, J=11.53 Hz, 2H), 7.40 (d, J=11.87 Hz, 2H), 7.60 (d, J=8.48 Hz, 2H), 7.83 (d, J=5.43 Hz, 1H), 8.67 (s, 1H), 8.86 (s, 1H); MS (ESI(+)) m/e 375 $(M+H)^+$.

Example 38

1-[4-(4-Amino-thieno[3,2-c]pyridin-3-yl)-phenyl]-3-(3-chloro-phenyl)-urea

X = 1-isocyanato-3-chlorobenzene. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.42 (s, 2H), 7.03-7.13 (m, 1H), 7.26 (d, J=5.76 Hz, 1H), 7.31-7.33 (m, 2H), 7.38 (d, J=8.48 Hz, 2H), 7.42 (s, 1H), 7.60 (d, J=8.48 Hz, 2H), 7.73 (d, J=1.70 Hz, 1H), 7.83 (d, J=5.76 Hz, 1H), 8.95 (s, 1H), 8.96 (s, 1H); MS (ESI(+)) m/e 395 $(M+H)^+$.

Example 39

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea

X = 1-isocyanato-2-fluoro-5-(trifluoromethyl)benzene. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.42 (s, 2H), 7.26 (d, *J*=5.76 Hz, 1H), 7.39 (s, 1H), 7.43 (d, *J*=5.43 Hz, 3H), 7.52-7.56 (m, 1H), 7.62 (d, *J*=8.48 Hz, 2H), 7.83 (d, *J*=5.76 Hz, 1H), 8.64 (dd, *J*=7.29, 1.86 Hz, 1H), 8.97 (d, *J*=2.37 Hz, 1H), 9.37 (s, 1H); MS (ESI(+)) m/e 447 $(M+H)^+$.

Example 40

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]-N'-[3-(trifluoromethyl)phenyl]urea

X = 1-isocyanato-3-(trifluoromethyl)benzene. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.42 (s, 2H), 7.26 (d, *J*=5.76 Hz, 1H), 7.33 (d, *J*=7.46 Hz, 1H), 7.39 (d, *J*=8.48 Hz, 2H), 7.43 (s, 1H), 7.53 (t, *J*=7.80 Hz, 1H), 7.59-7.63 (m, 3H), 7.83 (d, *J*=5.76 Hz, 1H), 8.04 (s, 1H), 9.00 (s, 1H), 9.12 (s, 1H); MS (ESI(+)) m/e 429 $(M+H)^+$.

Example 41

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]-N'-(3,5-dimethylphenyl)urea

X = 1-isocyanato-3,5-dimethylbenzene. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.24 (s, 6H), 5.42 (s, 2H), 6.63 (s, 1H), 7.09 (s, 2H), 7.25 (d, *J*=5.76 Hz, 1H), 7.36 (d, *J*=8.48 Hz, 2H), 7.42 (s, 1H), 7.59 (d, *J*=8.81 Hz, 2H), 7.82 (d, *J*=5.76 Hz, 1H), 8.57 (s, 1H), 8.83 (s, 1H); MS (ESI(+)) m/e 389 $(M+H)^+$.

Example 42

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]-N'-[4-fluoro-3-(trifluoromethyl)phenyl]urea

X = 1-isocyanato-4-fluoro-3-(trifluoromethyl)benzene. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.43 (s, 2H), 7.26 (d, *J*=5.76 Hz, 1H), 7.38 (d, *J*=8.48 Hz, 2H), 7.43 (s, 1H), 7.47 (d, *J*=10.17 Hz, 1H), 7.61 (d, *J*=8.48 Hz, 2H), 7.67-7.70 (m, 1H), 7.83 (d, *J*=5.76 Hz, 1H), 8.03 (dd, *J*=6.44, 2.71 Hz, 1H), 9.01 (s, 1H), 9.11 (s, 1H); MS (ESI(+)) m/e 447 $(M+H)^+$.

Example 43

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]-N'-1,3-benzodioxol-5-ylurea

X = 5-isocyanato-1,3-benzodioxole. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.42 (s, 2H), 5.98 (s, 2H), 6.78-6.80 (m, 1H), 6.85-6.87 (m, 1H), 7.22 (d, *J*=2.03 Hz, 1H), 7.25 (d, *J*=5.76 Hz, 1H), 7.36 (d, *J*=8.48 Hz, 2H), 7.41 (s, 1H), 7.58 (d, *J*=8.48 Hz, 2H), 7.82 (d, *J*=5.76 Hz, 1H), 8.62 (s, 1H), 8.80 (s, 1H); MS (ESI(+)) m/e 405 $(M+H)^+$.

Example 44

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]-N'-(3-nitrophenyl)urea

X = 1-isocyanato-3-nitrobenzene. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.42 (s, 2H), 7.26 (d, *J*=5.76 Hz, 1H), 7.40 (d, *J*=8.48 Hz, 2H), 7.43 (s, 1H), 7.63 (d, *J*=8.48 Hz, 3H),

7.74-7.76 (m, 1H), 7.83 (d, J=5.42 Hz, 2H), 8.58 (t, J=2.20 Hz, 1H), 9.05 (s, 1H), 9.30 (s, 1H); MS (ESI(+)) m/e 406 $(M+H)^+$.

Example 45

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]-N'-(3-chloro-4-methoxyphenyl)urea

X = 1-isocyanato-3-chloro-4-methoxybenzene. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.82 (s, 3H), 5.42 (s, 2H), 7.10 (d, J=9.16 Hz, 1H), 7.25 (d, J=5.43 Hz, 1H), 7.29 (dd, J=8.82, 2.71 Hz, 1H), 7.37 (d, J=8.48 Hz, 2H), 7.42 (s, 1H), 7.59 (d, J=8.82 Hz, 2H), 7.68 (d, J=2.37 Hz, 1H), 7.82 (d, J=5.76 Hz, 1H), 8.71 (s, 1H), 8.87 (s, 1H); MS (ESI(+)) m/e 425 $(M+H)^+$.

Example 46

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]-N'-(3,4-dimethylphenyl)urea

X = 1-isocyanato-3,4-dimethylbenzene. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.24 (s, 6H), 5.42 (s, 2H), 6.63 (s, 1H), 7.09 (s, 2H), 7.25 (d, J=5.43 Hz, 1H), 7.36 (d, J=8.48 Hz, 2H), 7.42 (s, 1H), 7.59 (d, J=8.48 Hz, 2H), 7.82 (d, J=5.43 Hz, 1H), 8.57 (s, 1H), 8.83 (s, 1H); MS (ESI(+)) m/e 389 $(M+H)^+$.

Example 47

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]-N'-[2-(trifluoromethyl)phenyl]urea

X = 1-isocyanato-2-(trifluoromethyl)benzene. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.41 (s, 2H), 7.26 (d, J=5.76 Hz, 1H), 7.30 (t, J=7.63 Hz, 1H), 7.39 (d, J=8.81 Hz, 2H), 7.43 (s, 1H), 7.61 (d, J=8.81 Hz, 2H), 7.69 (t, J=7.80 Hz, 2H), 7.83 (d, J=5.42 Hz, 1H), 7.96 (d, J=8.48 Hz, 1H), 8.15 (s, 1H), 9.56 (s, 1H); MS (ESI(+)) m/e 429 $(M+H)^+$.

Example 48

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea

X = 1-isocyanato-2-fluoro-5-methylbenzene. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.28 (s, 3H), 5.41 (s, 2H), 6.79-6.84 (m, 1H), 7.12 (dd, J=11.36, 8.31 Hz, 1H), 7.26 (d, J=5.43 Hz, 1H), 7.38 (d, J=8.48 Hz, 2H), 7.43 (s, 1H), 7.60 (d, J=8.48 Hz, 2H), 7.83 (d, J=5.43 Hz, 1H), 8.00 (dd, J=7.97, 2.20 Hz, 1H), 8.54 (d, J=2.71 Hz, 1H), 9.25 (s, 1H); MS (ESI(+)) m/e 393 $(M+H)^+$.

Example 49

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]-N'-(3-fluorophenyl)urea

X = 1-isocyanato-3-fluorobenzene. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.42 (s, 2H), 6.77-6.83 (m, 1H), 7.15 (dd, J=7.46, 2.03 Hz, 1H), 7.26 (d, J=5.76 Hz, 1H), 7.38 (d, J=8.81

Hz, 2H), 7.42 (s, 1H), 7.48-7.54 (m, 2H), 7.60-7.62 (m, 2H), 7.83 (d, J=5.42 Hz, 1H), 8.94 (s, 1H), 8.98 (s, 1H); MS (ESI(+)) m/e 379 $(M+H)^+$.

Example 50

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]-N'-(3-phenoxyphenyl)urea

X = 1-isocyanato-3-phenoxybenzene. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.41 (s, 2H), 6.61-6.65 (m, 1H), 7.03-7.05 (m, 2H), 7.15-7.20 (m, 2H), 7.24-7.30 (m, 3H), 7.34 (s, 1H), 7.38-7.44 (d, J=3.39 Hz, 2H), 7.42 (m, 2H), 7.56 (d, J=8.81 Hz, 2H), 7.82 (d, J=5.42 Hz, 1H), 8.84 (s, 1H), 8.87 (s, 1H); MS (ESI(+)) m/e 453 $(M+H)^+$.

Example 51

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]-N'-(3-cyanophenyl)urea

X = 1-isocyanato-3-cyanobenzene. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.42 (s, 2H), 7.26 (d, J=5.43 Hz, 1H), 7.39 (d, J=8.48 Hz, 2H), 7.43 (s, 1H), 7.50 (d, J=7.80 Hz, 2H), 7.61 (d, J=8.48 Hz, 2H), 7.69-7.72 (m, 1H), 7.83 (d, J=5.43 Hz, 1H), 8.00 (s, 1H), 9.05 (s, 1H), 9.10 (s, 1H); MS (ESI(+)) m/e 386 $(M+H)^+$.

Example 52

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]-N'-(2-fluorophenyl)urea

X = 1-isocyanato-2-fluorobenzene. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.42 (s, 2H), 7.04-7.06 (m, 1H), 7.15 (d, J=7.12 Hz, 1H), 7.26-7,28 (m, 2H), 7.39 (d, J=8.81 Hz, 2H), 7.43 (s, 1H), 7.60-7.62 (m, 2H), 7.83 (d, J=5.42 Hz, 1H), 8.17-8.20 (m, 1H), 8.62 (d, J=2.37 Hz, 1H), 9.27 (s, 1H); MS (ESI(+)) m/e 379 $(M+H)^+$.

Example 53

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]-N'-(3-chloro-4-methylphenyl)urea

X = 1-isocyanato-3-chloro-4-methylbenzene. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.27 (s, 3H), 5.42 (s, 2H), 7.25 (t, J=5.93 Hz, 3H), 7.37 (d, J=8.48 Hz, 2H), 7.42 (s, 1H), 7.59 (d, J=8.81 Hz, 2H), 7.71 (d, J=2.03 Hz, 1H), 7.82 (d, J=5.76 Hz, 1H), 8.84 (s, 1H), 8.91 (s, 1H) MS (ESI(+)) m/e 409 $(M+H)^+$.

Example 54

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]-N'-(4-ethylphenyl)urea

X = 1-isocyanato-4-ethylbenzene. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.19 (t, J=7.46 Hz, 3H), 2.58 (q, J=7.46 Hz, 2H), 5.42 (s, 2H), 6.84 (d, J=7.46 Hz, 1H), 7.19 (t, J=7.63 Hz, 1H), 7.25 (d, J=5.76 Hz, 2H), 7.34 (s, 1H), 7.37 (d, J=8.48 Hz, 2H), 7.42 (s, 1H), 7.60 (d, J=8.48 Hz, 2H), 7.82 (d, J=5.76 Hz, 1H), 8.67 (s, 1H), 8.84 (s, 1H); MS (ESI(+)) m/e 389

$(M+H)^+$.

Example 55

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]-N'-(4-fluorophenyl)urea

X = 1-isocyanato-4-fluorobenzene. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.42 (s, 2H), 7.14 (t, *J*=8.99 Hz, 2H), 7.26 (d, *J*=5.76 Hz, 1H), 7.37 (d, *J*=8.48 Hz, 2H), 7.42 (s, 1H), 7.49 (dd, *J*=9.16, 4.75 Hz, 2H), 7.59 (d, *J*=8.48 Hz, 2H), 7.82 (d, *J*=5.76 Hz, 1H), 8.77 (s, 1H), 8.86 (s, 1H); MS (ESI(+)) m/e 379 $(M+H)^+$.

Example 56

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]-N'-phenylurea

X = isocyanatobenzene. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.42 (s, 2H), 6.98 (t, *J*=7.46 Hz, 1H), 7.26 (d, *J*=5.76 Hz, 1H), 7.31 (d, *J*=7.80 Hz, 2H), 7.37 (d, *J*=8.48 Hz, 2H), 7.42 (s, 1H), 7.48 (d, *J*=7.80 Hz, 2H), 7.60 (d, *J*=8.48 Hz, 2H), 7.82 (d, *J*=5.43 Hz, 1H), 8.73 (s, 1H), 8.86 (s, 1H); MS (ESI(+)) m/e 361 $(M+H)^+$.

Example 57

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]-N'-(3-bromophenyl)urea

X = 1-isocyanato-3-bromobenzene. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.42 (s, 2H), 7.18-7.28 (m, 4H), 7.27 (s, 1H), 7.38-7.40 (m, 2H), 7.43 (s, 1H), 7.60 (d, *J*=8.81 Hz, 2H), 7.82 (d, *J*=5.76 Hz, 1H), 8.95 (s, 2H); MS (ESI(+)) m/e 440 $(M+H)^+$.

Example 58

N-(3-acetylphenyl)-N'-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]urea

X = 1-isocyanato-3-acetylbenzene. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.58 (s, 3H), 5.42 (s, 2H), 7.26 (d, *J*=5.76 Hz, 1H), 7.39 (d, *J*=8.48 Hz, 2H), 7.43 (s, 1H), 7.47 (d, *J*=7.80 Hz, 1H), 7.59-7.63 (m, 3H), 7.70 (dd, *J*=7.12, 2.37 Hz, 1H), 7.83 (d, *J*=5.76 Hz, 1H), 8.10 (d, *J*=2.03 Hz, 1H), 8.92 (s, 1H), 8.99 (s, 1H); MS (ESI(+)) m/e 403 $(M+H)^+$.

Example 59

methyl 3-[({[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]amino}carbonyl)amino]benzoate

X = methyl 3-isocyanatobenzoate. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.87 (s, 3H), 5.42 (s, 2H), 7.26 (d, *J*=5.76 Hz, 1H), 7.39 (d, *J*=8.82 Hz, 2H), 7.45-7.49 (m, 2H), 7.59 (d, *J*=8.82 Hz, 2H), 7.65-7.67 (m, 2H), 7.83 (d, *J*=5.43 Hz, 1H), 8.23 (t, *J*=1.87 Hz, 1H), 8.91 (s, 1H), 9.02 (s, 1H); MS (ESI(+)) m/e 419 $(M+H)^+$.

Example 60

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]-N'-2,3-dihydro-1H-inden-5-ylurea

X = 5-isocyanatoindane. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.96-2.05 (m, 2H), 2.77-2.86 (m, 4H), 5.42 (s, 2H), 7.13 (s, 1H), 7.15 (d, *J*=1.70 Hz, 1H), 7.25 (d, *J*=5.42 Hz, 1H), 7.36 (d, *J*=8.81 Hz, 2H), 7.39 (s, 1H), 7.41 (s, 1H), 7.59 (d, *J*=8.82 Hz, 2H), 7.82 (d, *J*=5.76 Hz, 1H), 8.59 (s, 1H), 8.81 (s, 1H); MS (ESI(+)) m/e 401 $(M+H)^+$.

Example 61

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]-N'-[4-(trifluoromethyl)phenyl]urea

X = 1-isocyanato-4-(trifluoromethyl)benzene. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.42 (s, 2H), 7.26 (d, *J*=5.76 Hz, 1H), 7.39 (d, *J*=8.48 Hz, 2H), 7.43 (s, 1H), 7.62 (d, *J*=8.48 Hz, 2H), 7.67 (d, *J*=4.75 Hz, 4H), 7.83 (d, *J*=5.43 Hz, 1H), 9.01 (s, 1H), 9.18 (s, 1H); MS (ESI(+)) m/e 429 $(M+H)^+$.

Example 62

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]-N'-(3-fluoro-4-methylphenyl)urea

X = 1-isocyanato-3-fluoro-4-methylbenzene. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.17 (d, *J*=1.36 Hz, 3H), 5.42 (s, 2H), 7.05 (dd, *J*=8.31, 2.20 Hz, 1H), 7.18 (t, *J*=8.48 Hz, 1H), 7.26 (d, *J*=5.42 Hz, 1H), 7.37 (d, *J*=8.48 Hz, 2H), 7.42 (s, 1H), 7.47 (d, *J*=2.03 Hz, 1H), 7.59 (d, *J*=8.48 Hz, 2H), 7.82 (d, *J*=5.76 Hz, 1H), 8.85 (s, 1H), 8.89 (s, 1H); MS (ESI(+)) m/e 393 $(M+H)^+$.

Example 63

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]-N'-(4-bromo-3-methylphenyl)urea

X = 1-isocyanato-4-bromo-3-methylbenzene. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.33 (s, 3H), 5.42 (s, 2H), 7.26 (d, *J*=5.76 Hz, 1H), 7.29 (d, *J*=2.37 Hz, 1H), 7.37 (d, *J*=8.82 Hz, 2H), 7.42 (s, 1H), 7.45-7.51 (m, 2H), 7.59 (d, *J*=8.82 Hz, 2H), 7.82 (d, *J*=5.76 Hz, 1H), 8.81 (s, 1H), 8.90 (s, 1H); MS (ESI(+)) m/e 454 $(M+H)^+$.

Example 64

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]-N'-[4-chloro-3-(trifluoromethyl)phenyl]urea

X = 1-isocyanato-4-chloro-3-(trifluoromethyl)benzene. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.42 (s, 2H), 7.26 (d, *J*=5.43 Hz, 1H), 7.39 (d, *J*=8.48 Hz, 2H), 7.43 (s, 1H), 7.60 (s, 1H), 7.64 (d, *J*=4.07 Hz, 2H), 7.66 (d, *J*=2.37 Hz, 1H), 7.83 (d, *J*=5.43 Hz, 1H), 8.13 (d, *J*=2.03 Hz, 1H), 9.05 (s, 1H), 9.24 (s, 1H); MS (ESI(+)) m/e 463 $(M+H)^+$.

Example 65

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]-N'-(3-chloro-4-fluorophenyl)urea

X = 1-isocyanato-3-chloro-4-fluorobenzene. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.42 (s, 2H), 7.26 (d, *J*=5.76 Hz, 1H), 7.357.39 (m, 3H), 7.41 (d, *J*=8.81 Hz, 2H), 7.60 (d, *J*=8.48 Hz, 2H), 7.82 (d, *J*=5.42 Hz, 2H), 8.95 (s, 1H), 8.97 (s, 1H); MS (ESI(+)) m/e 413 $(M+H)^+$.

Example 66

N-[4-(4-amino-2-methyl-7-nitrothieno[3,2-c]pyridin-3-yl)phenyl]-N'-(3-methylphenyl)urea

Example 66A

3-bromo-2-methylthieno[3,2-c]pyridin-4(5H)-one

The desired product was prepared by substituting 3-(4-bromo-5-methyl-2-thienyl)acrylic acid for (2E)-3-(4-bromo-2-thienyl)acrylic acid in Example 1A. MS (ESI(+)) m/e 245 $(M+H)^+$.

Example 66B

3-bromo-2-methyl-7-nitrothieno[3,2-c]pyridin-4(5H)-one

A solution of nitric acid (1.68 mL, 70%, 26. 8 mmol) in sulfuric acid (5 mL) was added dropwise to a 0 °C solution of Example 66A (3.27g, 13.4 mmol) in sulfuric acic (15 mL). The resulting mixture was stirred at 0 °C for 1 hour, warmed to room temperature overnight, and poured into ice water. The resulting precipitate was collected by filtration, washed with water, and dried in a vacuum oven to provide 2.47g (64 % yield) of the desired product. MS (ESI(+)) m/e 290 $(M+H)^+$.

Example 66C

3-bromo-2-methyl-7-nitrothieno[3,2-c]pyridin-4-amine

The desired product was prepared by substituting Example 66B for Example 1A in Example 1B. MS (ESI(+)) m/e 289 $(M+H)^+$.

Example 66D

N-(3-methylphenyl)-N'-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]urea

A 0 °C mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (5.03g, 23 mmol) and 1-isocyanato-3-methylbenzene (2.95 mL, 23 mmol) in THF (90 mL) was stirred at room temperature for 1 hour, concentrated, suspended in acetonitrile, and filtered. The filter cake was dried to provide 8.09g of the desired product.

Example 66E

N-[4-(4-amino-2-methyl-7-nitrothieno[3,2-c]pyridin-3-yl)phenyl]-N'-(3-methylphenyl)urea

The desired product was prepared by substituting Example 66C and Example 66D for

Example 1B and 4-phenoxyphenylboronic acid, respectively, in Example 10A. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 2.31 (s, 3H), 4.91 (br s, 2H), 6.81 (d, *J*=7.46 Hz, 1H), 7.17 (t, *J*=7.63 Hz, 1H), 7.26-7.27 (m, 1H), 7.30-7.33 (m, 3H), 7.66 (d, *J*=8.48 Hz, 2H), 8.68 (s, 1H), 8.91 (s, 1H), 8.93 (s, 1H); MS (ESI(+)) m/e 434 $(M+H)^+$.

Example 67

N-[4-(4-amino-2-methylthieno[3,2-c]pyridin-3-yl)phenyl]-N'-(3-methylphenyl)urea

Example 67A

3-bromo-2-methylthieno[3,2-c]pyridin-4-amine

The desired product was prepared by substituting Example 66A for Example 1A in Example 1B. MS (ESI(+)) m/e 244 $(M+H)^+$.

Example 67B

N-[4-(4-amino-2-methylthieno[3,2-c]pyridin-3-yl)phenyl]-N'-(3-methylphenyl)urea

The desired product was prepared by substituting Example 67A and Example 66D for Example 1B and 4-phenoxyphenylboronic acid, respectively, in Example 10A. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.26 (s, 3H), 2.29 (s, 3H), 5.18 (s, 2H), 6.81 (d, *J*=7.46 Hz, 1H), 7.17-7.25 (m, 2H), 7.30 (m, 4H), 7.62 (d, *J*=8.82 Hz, 2H), 7.75 (d, *J*=5.43 Hz, 1H), 8.66 (s, 1H), 8.86 (s, 1H); MS (ESI(+)) m/e 389 $(M+H)^+$.

Example 68

N-[4-(4-amino-2-methylthieno[3,2-c]pyridin-3-yl)phenyl]-N'-(3-chlorophenyl)urea

The desired product was prepared by substituting Example 67A and 4-({[(3-chlorophenyl)amino]carbonyl}amino)phenylboronic acid (prepared by substituting 1-isocyanato-3-chlorobenzene for 1-isocyanato-3-methylbenzene in Example 66D) for Example 1B and 4-phenoxyphenylboronic acid, respectively, in Example 10A. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.26 (s, 3H), 5.17 (s, 2H), 7.04-7.11 (m, 1H), 7.16 (d, *J*=5.43 Hz, 1H), 7.29 (d, *J*=8.48 Hz, 2H), 7.32 (d, *J*=3.39 Hz, 2H), 7.63 (d, *J*=8.82 Hz, 2H), 7.73 (s, 1H), 7.75 (d, *J*=5.43 Hz, 1H), 8.96 (s, 1H), 8.97 (s, 1H); MS (ESI(+)) m/e 409 $(M+H)^+$.

Example 69

N-[4-(4-amino-2-methylthieno[3,2-c]pyridin-3-yl)phenyl]-N'-(5,7-dimethyl-1,3-benzoxazol-2-yl)urea

Example 69A

N-(5,7-dimethyl-1,3-benzoxazol-2-yl)-N'-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

yl)phenyl]urea

A mixture of 1-bromo-4-isothiocyanatobenzene (63.92g, 0.298 mol) and THF (1200 mL) was treated with 2-amino-4,6-dimethylphenol (41.8g, 0.304 mol), stirred at room temperature for 3 hours, treated with EDCI (68.46g, 0.358 mol), warmed to 40 °C for 16 hours, cooled to room temperature, and filtered. The filtrate was concentrated at 50 °C to a final volume of about 300 mL, treated with acetonitrile (800 mL), concentrated to a volume of about 200 mL, treated with acetonitrile (800 mL), and again concentrated to a volume of about 200 mL. The mixture was treated with acetonitrile (800 mL), cooled to room temperature, and filtered. The filter cake was washed with acetonitrile (100 mL) and dried to constant weight in a vacuum oven at 45 °C over 24 hours to provide 85.8g (85%) of 5,7-dimethyl-1,3-benzoxazol-2-amine. A mixture of 5,7-dimethyl-1,3-benzoxazol-2-amine (76.4g, 0.230 mol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (73.9g, 0.292 mol), potassium acetate (71.5g, 0.730 mol), and DMF (760 mL) was cycled three times through vacuum degassing and nitrogen purging, treated with $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (19.9g, 0.024 mol), sealed, cycled three times through vacuum degassing and N_2 purging, heated to 80 °C for 5 hours, and distilled on high vacuum (0.2 mm Hg) at 40 °C to 80 °C to remove DMF. The residue was treated with CH_2Cl_2 (1300 mL), stirred for 10 minutes, and filtered. The filter cake was washed with CH_2Cl_2 (300 mL) and the filtrate was concentrated to a volume of about 800 mL. The solution was treated with SiO_2 (509 g), stirred for 10 minutes, poured onto a bed of SiO_2 (790 g) in a 4L coarse glass fritted funnel. The SiO_2 was washed with 16L of 15% ethyl acetate and the solution was concentarated at 50 °C. The concentrate was treated with heptane (800 mL), concentrated, treated with heptane (900 mL), stirred at 50 °C for 30 minutes, cooled to room temperature over 2 hours, and filtered. The filter cake was washed with 100 mL heptane and dried to constant weight in a vacuum oven at 45 °C over 24 hours to provide 68.3g (77%) of the desired product. The final product was determined to be 98.2% potency (vs. analytical standard) by HPLC. R_t = 6.5 min. HPLC conditions: Zorbax SB-C8 Rapid Resolution (4.6 mm x 75 mm, 3.5 um); flow 1.5 mL/min; 5:95 to 95:5 acetonitrile:water (0.1% H_3PO_4) over 7 minutes.

Example 69B

N-[4-(4-amino-2-methylthieno[3,2-c]pyridin-3-yl)phenyl]-N'-(5,7-dimethyl-1,3-benzoxazol-2-yl)urea

The desired product was prepared by substituting Example 67A and Example 69A for Example 1B and 4-phenoxyphenylboronic acid, respectively, in Example 10A. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.27 (s, 3H), 2.34 (s, 3H), 2.41 (s, 3H), 5.19 (s, 2H), 6.80 (s, 1H), 7.11 (s, 1H), 7.17 (d, *J*=5.42 Hz, 1H), 7.37 (d, *J*=8.48 Hz, 2H), 7.76 (d, *J*=5.76 Hz, 1H), 7.92

(d, J=8.48 Hz, 2H), 10.86 (s, 1H); MS (ESI(+)) m/e 401 $(M+H)^+$.

Example 70

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)phenyl]-N'-(5,7-dimethyl-1,3-benzoxazol-2-yl)urea

The desired product was prepared by substituting Example 66D for 4-phenoxyphenylboronic acid in Example 10A. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.34 (s, 3H), 2.40 (s, 3H), 5.41 (s, 2H), 6.79 (s, 1H), 7.11 (s, 1H), 7.26 (d, J=5.76 Hz, 1H), 7.44-7.50 (m, 2H), 7.48 (s, 1H), 7.83 (d, J=5.76 Hz, 1H), 7.89 (d, J=8.48 Hz, 2H), 10.84 (s, 1H); MS (ESI(+)) m/e 387 $(M+H)^+$.

Example 71

N-[4-(4,7-diamino-2-methylthieno[3,2-c]pyridin-3-yl)phenyl]-N'-(3-methylphenyl)urea

A suspension of Example 66E (0.44g, 1.01 mmol), NH_4Cl (0.054g, 1.01 mmol), and iron powder (0.45g, 8.1 mmol) in ethanol (16 mL) and water (4 mL) was heated at 80 °C for 3 hours, cooled to room temperature, and filtered through diatomaceous earth (Celite®). The pad was washed with ethyl acetate and ethanol and the filtrate was extracted three times with ethyl acetate. The combined extracts were washed with brine, dried (Na_2SO_4), flitered, and concentrated. The residue was purified by flash column chromatography on silica gel with 5% methanol/dichloromethane to provide 0.15 g of the desired product. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.27 (s, 3H), 2.29 (s, 3H), 4.48 (s, 2H), 4.59 (s, 2H), 6.80 (d, J=7.46 Hz, 1H), 7.17 (t, J=7.80 Hz, 1H), 7.25-7.29 (m, 3H), 7.30 (s, 1H), 7.31 (s, 1H), 7.60 (d, J=8.81 Hz, 2H), 8.67 (s, 1H), 8.86 (s, 1H); MS (ESI(+)) m/e 404 $(M+H)^+$.

Example 72

N-{4-amino-2-methyl-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}nicotinamide

Example 72A

tert-butyl 3-bromo-2-methyl-7-nitrothieno[3,2-c]pyridin-4-ylcarbamate

A 0 °C mixture of Example 66C (0.506g, 1.76 mmol) and NaH (111mg, 95% dispersion, 4.4 mmol) was stirred for 20 minutes, treated with a solution of di-tert-butyl dicarbonate (461mg, 2.1 mmol) in DMF (15 mL), stirred for an additional 2 hours at 0 °C, quenched with saturated aqueous NH_4Cl, and extracted three times with ethyl acetate. The combined extracts were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated to provide 0.605g of the desired product. MS (ESI(+)) m/e 389 $(M+H)^+$.

Example 72B

tert-butyl 7-amino-3-bromo-2-methylthieno[3,2-c]pyridin-4-ylcarbamate

The desired product was prepared by substituting Example 72A for Example 66E in Example 71. MS (ESI(+)) m/e 359 $(M+H)^+$.

Example 72C

tert-butyl 3-bromo-2-methyl-7-[(3-pyridinylcarbonyl)amino]thieno[3,2-c]pyridin-4-ylcarbamate

The desired product was prepared by substituting Example 72B and nicotinoyl chloride for Example 17A and acetyl chloride, respectively, in Example 17B. MS (ESI(-)) m/e 462 $(M-H)^-$.

Example 72D

N-{4-amino-2-methyl-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}nicotinamide

The desired product was prepared by substituting Example 72C and Example 66D for Example 1B and 4-phenoxyphenylboronic acid, respectively, in Example 10A. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.27 (s, 3H), 2.29 (s, 3H), 5.24 (s, 2H), 6.81 (d, J=7.46 Hz, 1H), 7.17 (t, J=7.80 Hz, 1H), 7.27 (d, J=11.53 Hz, 2H), 7.32 (s, 2H), 7.59 (d, J=5.09 Hz, 1H), 7.64 (d, J=8.48 Hz, 2H), 7.76 (s, 1H), 8.35 (d, J=7.80 Hz, 1H), 8.69 (s, 1H), 8.79 (d, J=5.76 Hz, 1H), 8.90 (s, 1H), 9.17 (s, 1H), 10.47 (s, 1H); MS (ESI(+)) m/e 509 $(M+H)^+$.

Example 73

N-{4-amino-2-methyl-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}-2-fluoro-5-(trifluoromethyl)benzamide

The desired product was prepared by substituting 2-fluoro-5-trifluromethylbenzoyl chloride for nicotinoyl chloride in Examples 72C-D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 6H), 5.36 (s, 2H), 6.81 (d, J=7.12 Hz, 1H), 7.17 (t, J=7.80 Hz, 1H), 7.27 (d, J=12.88 Hz, 2H), 7.32 (s, 2H), 7.64 (d, J=8.81 Hz, 3H), 7.83 (s, 1H), 8.04 (d, J=5.76 Hz, 1H), 8.09 (s, 1H), 8.69 (s, 1H), 8.91 (s, 1H), 10.46 (s, 1H); MS (ESI(+)) m/e 594 $(M+H)^+$.

Example 74

N-{4-amino-2-methyl-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}-3-(dimethylamino)benzamide

The desired product was prepared by substituting 3-dimethylaminobenzoyl chloride for nicotinoyl chloride in Examples 72C-D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.26 (s, 3H), 2.29 (s, 3H), 2.98 (s, 6H), 5.20 (s, 2H), 6.81 (d, J=7.46 Hz, 1H), 6.95 (d, J=7.46 Hz, 1H), 7.17 (t, J=7.63 Hz, 1H), 7.27 (d, J=10.85 Hz, 2H), 7.31 (s, 5H), 7.64 (d, J=8.48 Hz, 2H),

7.71 (s, 1H), 8.67 (s, 1H), 8.87 (s, 1H), 10.14 (s, 1H); MS (ESI(+)) m/e 551 $(M+H)^+$.

Example 75

N-{4-amino-2-methyl-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}pentanamide

The desired product was prepared by substituting pentanoyl chloride for nicotinoyl chloride in Examples 72C-D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.94 (t, J=7.29 Hz, 3H), 1.33-1.45 (m, 2H), 1.57-1.67 (m, 2H), 2.25 (s, 3H), 2.29 (s, 3H), 2.33 (t, J=7.29 Hz, 2H), 5.13 (s, 2H), 6.81 (d, J=7.12 Hz, 1H), 7.17 (t, J=7.63 Hz, 1H), 7.25 (d, J=3.05 Hz, 2H), 7.30 (d, J=8.82 Hz, 2H), 7.62 (d, J=4.07 Hz, 2H), 7.64 (s, 1H), 8.67 (s, 1H), 8.87 (s, 1H), 9.64 (s, 1H); MS (ESI(+)) m/e 488 $(M+H)^+$.

Example 76

N-[4-(4-amino-7-bromothieno[3,2-c]pyridin-3-yl)phenyl]-N'-(3-methylphenyl)urea

Example 76A

tert-butyl 4-(4-aminothieno[3,2-c]pyridin-3-yl)phenylcarbamate

The desired product was prepared by substituting Example 17A for Example 66C in Example 72A. MS (ESI(-)) m/e 340 $(M-H)^-$.

Example 76B

tert-butyl 4-(4-amino-7-bromothieno[3,2-c]pyridin-3-yl)phenylcarbamate

A solution of bromine (0.4 mL, 4.6 mmol) in dichloromethane (5 mL) was added dropwise to a -5 °C solution of Example 76A (1.57g, 4.6 mmol) in dichloromethane (30 mL). The mixture was stirred at –5 °C to 0 °C for 15 minutes and quenched with 1:1 saturated $NaHCO_3$ and saturated $NaHSO_3$ (10 mL). The organic phase was separated, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated to provide 1.85g of the desired product. MS (ESI(+)) m/e 421 $(M+H)^+$.

Example 76C

3-(4-aminophenyl)-7-bromothieno[3,2-c]pyridin-4-amine

A solution of Example 76B (0.5g, 1.1 mmol) in TFA (4 mL) and dichloromethane (5 mL) was stirred at 0 °C for 5 minutes, warmed to room temperature for 2 hours, then concentrated. The residue was dissolved in dichloromethane, washed with brine, dried (Na_2SO_4), filtered, and concentrated to provide 0.332g of the desired product. MS (ESI(+)) m/e 321 $(M+H)^+$.

Example 76D

N-[4-(4-amino-7-bromothieno[3,2-c]pyridin-3-yl)phenyl]-N'-(3-methylphenyl)urea

The desired product was prepared by substituting Example 76C for Example 1C in Example 1D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 5.62 (s, 2H), 6.81 (d, J=7.46 Hz, 1H), 7.17 (t, J=7.63 Hz, 1H), 7.25-7.27 (m, 1H), 7.31 (s, 1H), 7.38 (d, J=8.48 Hz, 2H), 7.56 (s, 1H), 7.60 (d, J=8.48 Hz, 2H), 7.94 (s, 1H), 8.66 (s, 1H), 8.87 (s, 1H); MS (ESI(+)) m/e 454 $(M+H)^+$.

Example 77

tert-butyl (2E)-3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}acrylate

Example 77A

tert-butyl 4-(4-amino-7-iodothieno[3,2-c]pyridin-3-yl)phenylcarbamate

The desired product was prepared by substituting Example 76A for Example 10A in Example 10B. MS (ESI(+)) m/e 468 $(M+H)^+$.

Example 77B

3-(4-aminophenyl)-7-iodothieno[3,2-c]pyridin-4-amine

The desired product was prepared by substituting Example 77A for Example 76B in Example 76C. MS (ESI(+)) m/e 368 $(M+H)^+$.

Example 77C

tert-butyl (2E)-3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}acrylate

The desired product was prepared by substituting Example 77B for Example 10B in Example 11A then substituting the product for Example 1C in Example 1D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.51 (s, 9H), 2.29 (s, 3H), 6.03 (s, 2H), 6.32 (d, J=15.94 Hz, 1H), 6.81 (d, J=7.46 Hz, 1H), 7.17 (t, J=7.80 Hz, 1H), 7.26-7.27 (m, 1H), 7.32 (s, 1H), 7.40 (d, J=8.48 Hz, 2H), 7.60 (d, J=3.73 Hz, 2H), 7.63 (s, 1H), 7.72 (d, J=15.94 Hz, 1H), 8.23 (s, 1H), 8.67 (s, 1H), 8.87 (s, 1H); MS (ESI(+)) m/e 501 $(M+H)^+$.

Example 78

(2E)-3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}acrylic acid

The desired product was prepared by substituting Example 77C for Example 11A in Example 11B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 5.09 (s, 2H), 6.59 (d, J=16.28

Hz, 1H), 6.81 (d, J=7.80 Hz, 1H), 7.10 (s, 1H), 7.17 (t, J=7.63 Hz, 1H), 7.25-7.29 (m, 1H), 7.32 (s, 1H), 7.44 (d, J=8.48 Hz, 2H), 7.66 (d, J=8.82 Hz, 2H), 7.76 (d, J=16.28 Hz, 1H), 7.90 (s, 1H), 8.37 (s, 1H), 8.80 (s, 1H), 9.06 (s, 1H); MS (ESI(+)) m/e 445 $(M+H)^+$.

Examples 79-103 were prepared by substituting the appropriate amine (X), Example 78B, and TBTU for 2-piperazinone, Example 11B, and HOBT, respectively, in Example 11C.

Example 79

(2E)-3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}-N,N-dimethylacrylamide

X = dimethylamine hydrochloride. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 2.97 (s, 3H), 3.19 (s, 3H), 5.90 (s, 2H), 6.81 (d, J=7.46 Hz, 1H), 7.02 (d, J=15.60 Hz, 1H), 7.17 (t, J=7.80 Hz, 1H), 7.26-7.28 (m, 1H), 7.32 (s, 1H), 7.39 (d, J=8.48 Hz, 2H), 7.60-7.62 (m, 2H), 7.65-7.68 (m, 1H), 7.95 (s, 1H), 8.25 (s, 1H), 8.66 (s, 1H), 8.87 (s, 1H); MS (ESI(+)) m/e 472 $(M+H)^+$.

Example 80

N-(4-{4-amino-7-[(1E)-3-oxo-3-(3-oxo-1-piperazinyl)-1-propenyl]thieno[3,2-c]pyridin-3-yl}phenyl)-N'-(3-methylphenyl)urea

X =2-piperazinone. The product was prepared as the trifluoroacetate salt by purifying the crude product as described in Example 82. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 3.81 (d, J=36.96 Hz, 4H), 4.21 (d, J=65.77 Hz, 2H), 6.81 (d, J=7.46 Hz, 1H), 6.88 (s, 2H), 7.17-7.20 (m, 1H), 7.26-7.28 (m, 2H), 7.32 (s, 1H), 7.44 (d, J=8.48 Hz, 2H), 7.64 (s, 2H), 7.68-7.70 (m, 1H), 7.85 (s, 1H), 8.16 (s, 1H), 8.41 (s, 1H), 8.76 (s, 1H), 9.01 (s, 1H); MS (ESI(+)) m/e 527 $(M+H)^+$.

Example 81

(2E)-3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}-N-(2-pyridinylmethyl)acrylamide

X = 1-(2-pyridinyl)methanamine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 4.52 (d, J=6.10 Hz, 2H), 5.91 (s, 2H), 6.73 (d, J=15.94 Hz, 1H), 6.81 (d, J=7.12 Hz, 1H), 7.17 (t, J=7.80 Hz, 1H), 7.24-7.36 (m, 4H), 7.40 (d, J=8.48 Hz, 2H), 7.61 (d, J=3.73 Hz, 2H), 7.65-7.67 (m, 2H), 7.78-7.81 (m, 1H), 8.14 (s, 1H), 8.53 (d, J=4.75 Hz, 1H), 8.66 (s, 1H), 8.83 (t, J=5.93 Hz, 1H), 8.87 (s, 1H); MS (ESI(+)) m/e 535 $(M+H)^+$.

Example 82

3-[((2E)-3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-

c]pyridin-7-yl}-2-propenoyl)amino]-2-thiophenecarboxamide

X= 3-amino-2-thiophenecarboxamide. The product was prepared as the trifluoroacetate salt by preparative HPLC purification on a Waters Symmetry C8 column (25mm x 100mm, 7μm particle size) using a gradient of 10% to 100% acetonitrile/0.1% aqueous TFA over 8 minutes (10 minute run time) at a flow rate of 40mL/min. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 3.87 (s, 2H), 6.81 (d, J=7.46 Hz, 1H), 6.88-6.96 (m, 2H), 7.17 (t, J=7.80 Hz, 1H), 7.26-7.29 (m, 1H), 7.32 (s, 1H), 7.45 (d, J=8.82 Hz, 2H), 7.66 (d, J=8.48 Hz, 3H), 7.77 (dd, J=10.51, 5.09 Hz, 2H), 7.86 (s, 1H), 8.07 (d, J=5.43 Hz, 1H), 8.42 (s, 1H), 8.77 (s, 1H), 9.02 (s, 1H), 11.49 (s, 1H); MS (ESI(+)) m/e 569 $(M+H)^+$.

Example 83

(2E)-3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}-N-[2-(4-morpholinyl)ethyl]acrylamide

X = 2-(4-morpholinyl)ethanamine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 2.43 (t, J=6.10 Hz, 4H), 3.32-3.37 (m, 5H), 3.59-3.61 (m, 4H), 5.87 (s, 2H), 6.62 (d, J=15.94 Hz, 1H), 6.81 (d, J=7.12 Hz, 1H), 7.17 (t, J=7.80 Hz, 1H), 7.26-7.28 (m, 1H), 7.32 (s, 1H), 7.40 (d, J=8.82 Hz, 2H), 7.55-7.63 (m, 3H), 8.12 (s, 1H), 8.18 (t, J=5.59 Hz, 1H), 8.67 (s, 1H), 8.87 (s, 1H); MS (ESI(+)) m/e 557 $(M+H)^+$.

Example 84

(2E)-3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}-N-[3-(1-pyrrolidinyl)propyl]acrylamide

X= 3-(1-pyrrolidinyl)-1-propanamine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.67-1.70 (m, 5H), 2.29 (s, 3H), 3.28-3.37 (m, 9H), 5.86 (s, 2H), 6.59 (d, J=15.94 Hz, 1H), 6.81 (d, J=7.12 Hz, 1H), 7.17 (t, J=7.63 Hz, 1H), 7.26-7.28 (m, 1H), 7.32 (s, 1H), 7.40 (d, J=8.48 Hz, 2H), 7.55-7.63 (m, 4H), 8.11 (s, 1H), 8.23 (t, J=5.43 Hz, 1H), 8.67 (s, 1H), 8.88 (s, 1H); MS (ESI(+)) m/e 555 $(M+H)^+$.

Example 85

(2E)-3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}-N-[(1-ethyl-2-pyrrolidinyl)methyl]acrylamide

X= (1-ethyl-2-pyrrolidinyl)methylamine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.06 (t, J=7.29 Hz, 3H), 1.53-1.87(m, 4H), 2.07-2.27 (m, 2H), 2.29 (s, 3H), 2.84-2.87 (m, 2H), 3.02-3.08 (m, 2H), 3.39-3.47 (m, 1H), 5.87 (s, 2H), 6.66 (d, J=15.94 Hz, 1H), 6.81 (d, J=7.46 Hz, 1H), 7.17 (t, J=7.63 Hz, 1H), 7.26-7.28 (m, 1H), 7.32 (s, 1H), 7.40 (d, J=8.48 Hz, 2H), 7.55-7.63 (m, 4H), 8.10 (d, J=7.46 Hz, 2H), 8.67 (s, 1H), 8.88 (s, 1H); MS (ESI(+)) m/e 555 $(M+H)^+$.

Example 86

(2E)-3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}-N-[2-(diethylamino)ethyl]acrylamide

X= N,N-diethyl-1,2-ethanediamine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.97 (t, J=7.12 Hz, 6H), 2.29 (s, 3H), 2.51-2.55 (m, 4H), 3.27-3.29 (m, 4H), 5.87 (s, 2H), 6.61 (d, J=15.94 Hz, 1H), 6.81 (d, J=7.12 Hz, 1H), 7.17 (t, J=7.63 Hz, 1H), 7.26-7.28 (m, 1H), 7.32 (s, 1H), 7.40 (d, J=8.48 Hz, 2H), 7.55-7.63 (m, 4H), 8.11 (s, 1H), 8.14-8.17 (m, 1H), 8.67 (s, 1H), 8.87 (s, 1H); MS (ESI(+)) m/e 543 $(M+H)^+$.

Example 87

(2E)-3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}-N-(2-hydroxyethyl)acrylamide

X= 2-aminoethanol. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 3.29-3.37 (m, 2H), 3.49 (q, J=5.88 Hz, 2H), 4.75 (t, J=5.43 Hz, 1H), 5.87 (s, 2H), 6.64 (d, J=15.94 Hz, 1H), 6.80 (d, J=7.46 Hz, 1H), 7.16 (t, J=7.80 Hz, 1H), 7.28 (d, J=8.14 Hz, 1H), 7.31 (s, 1H), 7.39 (d, J=8.48 Hz, 2H), 7.61-7.64 (m, 4H), 8.11 (s, 1H), 8.28 (t, J=5.76 Hz, 1H), 9.09 (s, 1H), 9.35 (s, 1H); MS (ESI(+)) m/e 488 $(M+H)^+$.

Example 88

(2E)-3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}-N-(3-pyridinylmethyl)acrylamide

X= 1-(3-pyridinyl)methanamine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 4.45 (d, J=5.76 Hz, 2H), 5.90 (s, 2H), 6.65 (d, J=15.94 Hz, 1H), 6.81 (d, J=7.46 Hz, 1H), 7.17 (t, J=7.80 Hz, 1H), 7.26-7.28 (m, 1H), 7.32 (s, 1H), 7.39-7.41 (m, 2H), 7.63-7.67 (m, 5H), 7.73 (d, J=7.80 Hz, 1H), 8.13 (s, 1H), 8.48 (dd, J=4.75, 1.70 Hz, 1H), 8.56 (d, J=2.03 Hz, 1H), 8.66 (s, 1H), 8.78 (t, J=5.76 Hz, 1H), 8.87 (s, 1H); MS (ESI(+)) m/e 535 $(M+H)^+$.

Example 89

(2E)-3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}-N-(2,3-dihydroxypropyl)acrylamide

X= 3-amino-1,2-propanediol. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 3.12-3.37 (m, 4H), 3.58-3.60 (m, 1H), 4.59 (t, J=5.76 Hz, 1H), 4.83 (d, J=4.75 Hz, 1H), 5.87 (s, 2H), 6.69 (d, J=15.94 Hz, 1H), 6.81 (d, J=7.12 Hz, 1H), 7.17 (t, J=7.80 Hz, 1H), 7.26-7.28 (m, 1H), 7.32 (s, 1H), 7.40 (d, J=8.48 Hz, 2H), 7.56-7.63 (m, 4H), 8.12 (s, 1H), 8.26 (t, J=5.76 Hz, 1H), 8.67 (s, 1H), 8.87 (s, 1H); MS (ESI(-)) m/e 516 $(M-H)^-$.

Example 90

(2E)-3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}-N-(4-pyridinylmethyl)acrylamide

X= 1-(4-pyridinyl)methanamine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 4.46 (d, J=5.76 Hz, 2H), 5.92 (s, 2H), 6.69 (d, J=15.94 Hz, 1H), 6.81 (d, J=7.46 Hz, 1H), 7.17 (t, J=7.80 Hz, 1H), 7.26-7.28 (m, 1H), 7.31 (d, J=5.76 Hz, 3H), 7.40 (d, J=8.82 Hz, 2H), 7.64-7.68 (m, 4H), 8.15 (s, 1H), 8.52 (d, J=1.70 Hz, 1H), 8.53 (d, J=1.70 Hz, 1H), 8.67 (s, 1H), 8.83 (t, J=6.10 Hz, 1H), 8.87 (s, 1H); MS (ESI(+)) m/e 535 $(M+H)^+$.

Example 91

N-(4-{4-amino-7-[(1E)-3-oxo-3-(1-piperazinyl)-1-propenyl]thieno[3,2-c]pyridin-3-yl}phenyl)-N'-(3-methylphenyl)urea

X= piperazine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 3.63-3.90 (m, 8H), 6.66 (s, 2H), 6.81 (d, J=6.78 Hz, 1H), 7.22-7.28 (m, 2H), 7.33 (s, 1H), 7.42 (d, J=7.12 Hz, 2H), 7.65 (d, J=6.10 Hz, 2H), 7.75 (d, J=21.36 Hz, 2H), 8.38 (s, 1H), 8.86 (s, 3H), 9.10 (s, 1H); MS (ESI(+)) m/e 513 $(M+H)^+$.

Example 92

(2E)-3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}-N-[3-(2-oxo-1-pyrrolidinyl)propyl]acrylamide

X= 1-(3-aminopropyl)-2-pyrrolidinone. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.67-1.72 (m, 2H), 1.93-1.98 (m, 2H), 2.22 (t, J=7.97 Hz, 2H), 2.29 (s, 3H), 3.15-3.38 (m, 6H), 5.87 (s, 2H), 6.59 (d, J=15.94 Hz, 1H), 6.81 (d, J=7.12 Hz, 1H), 7.17 (t, J=7.63 Hz, 1H), 7.26-7.28 (m, 1H), 7.32 (s, 1H), 7.40 (d, J=8.48 Hz, 2H), 7.56-7.63 (m, 4H), 8.12 (s, 1H), 8.21 (t, J=5.60 Hz, 1H), 8.66 (s, 1H), 8.87 (s, 1H); MS (ESI(+)) m/e 569 $(M+H)^+$.

Example 93

(2E)-3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}-N-phenylacrylamide

X= aniline. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 5.97 (s, 2H), 6.79-8.84 (m, 2H), 7.07 (t, J=7.29 Hz, 1H), 7.17 (t, J=7.80 Hz, 1H), 7.25-7.27 (m, 1H), 7.35-7.37 (m, 3H), 7.41 (d, J=8.48 Hz, 2H), 7.63 (d, J=8.48 Hz, 2H), 7.68 (s, 1H), 7.74-7.75 (m, 2H), 7.78 (s, 1H), 8.19 (s, 1H), 8.79 (s, 1H), 9.02 (s, 1H), 10.28 (s, 1H); MS (ESI(-)) m/e 518 $(M-H)^-$.

Example 94

(2E)-3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}-N-3-pyridinylacrylamide

X= 3-pyridinamine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 6.02 (s, 2H), 6.79 (d, *J*=5.09 Hz, 2H), 6.83 (d, *J*=3.39 Hz, 1H), 7.17 (t, *J*=7.80 Hz, 1H), 7.26-7.27 (m, 1H), 7.32 (s, 1H), 7.40-7.43 (m, 2H), 7.62-7.65 (m, 2H), 7.69 (s, 1H), 7.80 (d, *J*=15.93 Hz, 1H), 8.18-8.20 (m, 1H), 8.21 (s, 1H), 8.28 (dd, *J*=4.75, 1.36 Hz, 1H), 8.68 (s, 1H), 8.87 (d, *J*=2.03 Hz, 1H), 8.89 (s, 1H), 10.49 (s, 1H); MS (ESI(-)) m/e 519 $(M-H)^-$.

Example 95

N-((2E)-3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}-2-propenoyl)glycinamide

X=glycinamide. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 3.80 (d, *J*=5.76 Hz, 2H), 5.89 (s, 2H), 6.70 (d, *J*=15.94 Hz, 1H), 6.81 (d, *J*=7.12 Hz, 1H), 7.03 (s, 1H), 7.17 (t, *J*=7.63 Hz, 1H), 7.26-7.27 (m, 1H), 7.32 (s, 1H), 7.40 (d, *J*=8.48 Hz, 3H), 7.59 (d, *J*=8.82 Hz, 2H), 7.63 (s, 2H), 8.13 (s, 1H), 8.43 (t, *J*=5.76 Hz, 1H), 8.67 (s, 1H), 8.87 (s, 1H); MS (ESI(+)) m/e 501 $(M+H)^+$.

Example 96

(2E)-3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}-N-[3-(1H-imidazol-1-yl)propyl]acrylamide

X= 3-(1H-imidazol-1-yl)-1-propanamine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.89-1.99 (m, 2H), 2.29 (s, 3H), 3.18 (dd, *J*=12.55, 6.78 Hz, 2H), 4.05 (t, *J*=6.95 Hz, 2H), 5.90 (s, 2H), 6.59 (d, *J*=15.94 Hz, 1H), 6.81 (d, *J*=7.46 Hz, 1H), 7.00 (s, 1H), 7.17 (t, *J*=7.80 Hz, 1H), 7.26 (d, *J*=8.48 Hz, 2H), 7.31 (d, *J*=7.46 Hz, 2H), 7.40 (d, *J*=8.48 Hz, 2H), 7.59 (d, *J*=8.82 Hz, 2H), 7.63 (s, 1H), 7.84 (s, 1H), 8.13 (s, 1H), 8.30 (t, *J*=5.59 Hz, 1H), 8.67 (s, 1H), 8.88 (s, 1H); MS (ESI(+)) m/e 552 $(M+H)^+$.

Example 97

tert-butyl N-((2E)-3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}-2-propenoyl)-β-alaninate

X=tert-butyl β-alaninate. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.42 (s, 9H), 2.29 (s, 3H), 2.45 (t, *J*=6.78 Hz, 2H), 3.36-3.42 (m, 2H), 5.89 (s, 2H), 6.59 (d, *J*=15.94 Hz, 1H), 6.81 (d, *J*=7.12 Hz, 1H), 7.17 (t, *J*=7.80 Hz, 1H), 7.26-7.28 (m, 1H), 7.32 (s, 1H), 7.40 (d, *J*=8.48 Hz, 2H), 7.56-7.63 (m, 4H), 8.12 (s, 1H), 8.30 (t, *J*=5.59 Hz, 1H), 8.68 (s, 1H), 8.88 (s, 1H); MS (ESI(+)) m/e 572 $(M+H)^+$.

Example 98

N-(4-{4-amino-7-[(1E)-3-(4-morpholinyl)-3-oxo-1-propenyl]thieno[3,2-c]pyridin-3-

yl}phenyl)-N'-(3-methylphenyl)urea

X= morpholine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 3.64 (s, 8H), 5.93 (s, 2H), 6.81 (d, *J*=7.46 Hz, 1H), 7.05 (d, *J*=15.26 Hz, 1H), 7.17 (t, *J*=7.80 Hz, 1H), 7.23-7.27 (m, 1H), 7.32 (s, 1H), 7.39 (d, *J*=8.48 Hz, 2H), 7.58 (s, 1H), 7.62 (d, *J*=8.48 Hz, 2H), 7.70 (d, *J*=15.60 Hz, 1H), 8.29 (s, 1H), 8.67 (s, 1H), 8.88 (s, 1H); MS (ESI(+)) m/e 514 $(M+H)^+$.

Example 99

(2E)-3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}-N-methylacrylamide

X=methylamine hydrochloride. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 2.73 (s, 3H), 5.87 (s, 2H), 6.58 (d, *J*=15.94 Hz, 1H), 6.81 (d, *J*=7.12 Hz, 1H), 7.17 (t, *J*=7.63 Hz, 1H), 7.26-7.28 (m, 1H), 7.32 (s, 1H), 7.39 (d, *J*=8.48 Hz, 2H), 7.62-7.65 (m, 4H), 8.11 (s, 1H), 8.16 (d, *J*=4.75 Hz, 1H), 8.77 (s, 1H), 8.99 (s, 1H); MS (ESI(+)) m/e 458 $(M+H)^+$.

Example 100

(2E)-3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}acrylamide

X= ammonia. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 5.88 (s, 2H), 6.58 (d, *J*=16.27 Hz, 1H), 6.81 (d, *J*=7.12 Hz, 1H), 7.05 (s, 1H), 7.17 (t, *J*=7.46 Hz, 1H), 7.25-7.27 (m, 1H), 7.32 (s, 1H), 7.40 (d, *J*=8.14 Hz, 2H), 7.60-7.62 (m, 5H), 8.11 (s, 1H), 8.67 (s, 1H), 8.87 (s, 1H); MS (ESI(+)) m/e 444 $(M+H)^+$.

Example 101

N-(4-{4-amino-7-[(1E)-3-(5-amino-1H-pyrazol-1-yl)-3-oxo-1-propenyl]thieno[3,2-c]pyridin-3-yl}phenyl)-N'-(3-methylphenyl)urea

X = 1H-pyrazol-5-amine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.73-1.75 (m, 1H), 2.29 (s, 3H), 3.02-3.07 (m, 1H), 3.58 (s, 2H), 6.02 (d, *J*=2.71 Hz, 1H), 6.81 (d, *J*=7.46 Hz, 1H), 7.17 (t, *J*=7.63 Hz, 1H), 7.27-7.29 (m, 1H), 7.33 (s, 1H), 7.45 (d, *J*=8.48 Hz, 2H), 7.66 (d, *J*=8.82 Hz, 2H), 7.80 (d, *J*=16.28 Hz, 1H), 7.88 (s, 1H), 8.02 (d, *J*=16.27 Hz, 1H), 8.19 (d, *J*=3.05 Hz, 1H), 8.42 (s, 1H), 8.76 (s, 1H), 9.01 (s, 1H); MS (ESI(+)) m/e 510 $(M+H)^+$.

Example 102

tert-butyl N-((2E)-3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}-2-propenoyl)glycinate

X= tert-butyl glycinate. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.44 (s, 9H), 2.29 (s, 3H), 3.88 (d, *J*=6.10 Hz, 2H), 5.91 (s, 2H), 6.66 (d, *J*=16.28 Hz, 1H), 6.81 (d, *J*=7.12 Hz, 1H),

7.17 (t, J=7.80 Hz, 1H), 7.26-7.28 (m, 1H), 7.32 (s, 1H), 7.40 (d, J=8.48 Hz, 2H), 7.60 (d, J=3.73 Hz, 2H), 7.64-7.66 (m, 2H), 8.14 (s, 1H), 8.59 (t, J=5.93 Hz, 1H), 8.77 (s, 1H), 8.99 (s, 1H); MS (ESI(+)) m/e 558 $(M+H)^+$.

Example 103

N-((2E)-3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}-2-propenoyl)-β-alanine

The desired product was prepared by substituting Example 97 for Example 11A in Example 11B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 2.48 (d, J=10.85 Hz, 2H), 3.41 (q, J=6.44 Hz, 2H), 6.75 (s, 1H), 6.82-6.87 (m, 4H), 7.17 (t, J=7.80 Hz, 1H), 7.26-7.29 (m, 1H), 7.33 (s, 1H), 7.44 (d, J=8.81 Hz, 2H), 7.58-7.64 (m, 2H), 7.67 (s, 1H), 7.90 (s, 1H), 8.23 (s, 1H), 8.46 (t, J=5.59 Hz, 1H), 8.81 (s, 1H), 9.06 (s, 1H); MS (ESI(+)) m/e 516 $(M+H)^+$.

Example 104

N-((2E)-3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}-2-propenoyl)glycine

The desired product was prepared as the trifluoroacetate salt by substituting Example 102 for Example 11A in Example 11B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 3.94 (d, J=5.76 Hz, 2H), 4.95 (s, 2H), 6.81 (d, J=7.46 Hz, 1H), 6.90 (d, J=16.28 Hz, 1H), 7.16 (dd, J=16.28, 8.48 Hz, 2H), 7.27-7.29 (m, 1H), 7.33 (s, 1H), 7.45 (d, J=8.48 Hz, 2H), 7.62-7.69 (m, 3H), 7.96 (d, J=5.43 Hz, 1H), 8.29 (s, 1H), 8.75 (t, J=5.76 Hz, 1H), 8.92 (s, 1H), 9.18 (s, 1H); MS (ESI(+)) m/e 502 $(M+H)^+$.

Example 105

tert-butyl 3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}propanoate

The desired product was prepared by substituting Example 77 for Example 14 in Example 15. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.38 (s, 9H), 2.29 (s, 3H), 2.63 (t, J=7.29 Hz, 2H), 2.93 (t, J=7.46 Hz, 2H), 5.31 (s, 2H), 6.80 (d, J=7.46 Hz, 1H), 7.17 (t, J=7.80 Hz, 1H), 7.25-7.27 (m, 1H), 7.31 (s, 1H), 7.34-7.37 (m, 2H), 7.44 (s, 1H), 7.59 (d, J=8.81 Hz, 2H), 7.68 (s, 1H), 8.67 (s, 1H), 8.87 (s, 1H); MS (ESI(+)) m/e 503 $(M+H)^+$.

Example 106

3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}propanoic acid

The desired product was prepared as the trifluoroacetate salt by substituting Example

105 for 11A in Example 11B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 2.74 (t, *J*=7.29 Hz, 2H), 3.02 (t, *J*=7.46 Hz, 2H), 3.85 (s, 1H), 6.81 (d, *J*=7.46 Hz, 1H), 6.96 (s, 2H), 7.17 (t, *J*=7.63 Hz, 1H), 7.26-7.27 (m, 1H), 7.32 (s, 1H), 7.44 (d, *J*=8.48 Hz, 2H), 7.66 (d, *J*=8.48 Hz, 2H), 7.76 (s, 1H), 7.89 (s, 1H), 8.82 (s, 1H), 9.08 (s, 1H); MS (ESI(+)) m/e 447 $(M+H)^+$.

Example 107

3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}-N-[2-(4-morpholinyl)ethyl]propanamide

The desired product was prepared by substituting 2-(4-morpholinyl)ethanamine, Example 106, and TBTU for 2-piperazinone, Example 11B, and HOBT, respectively, in Example 11C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.31-2.36 (m, 9H), 2.92 (m, 2H), 3.16 (q, *J*=6.67 Hz, 2H), 3.26-3.37 (m, 2H), 3.54-3.56 (m, 4H), 5.27 (s, 2H), 6.80 (d, *J*=7.46 Hz, 1H), 7.17 (t, *J*=7.63 Hz, 1H), 7.25-7.27 (m, 1H), 7.31 (s, 1H), 7.35 (d, *J*=8.48 Hz, 2H), 7.44 (s, 1H), 7.59 (d, *J*=8.48 Hz, 2H), 7.66 (s, 1H), 7.80 (t, *J*=5.59 Hz, 1H), 8.65 (s, 1H), 8.84 (s, 1H); MS (ESI(+)) m/e 559 $(M+H)^+$.

Example 108

3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}-N-methylpropanamide

The desired product was prepared by substituting methylamine, Example 106, and TBTU for 2-piperazinone, Example 11B, and HOBT, respectively, in Example 11C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 2.57 (d, *J*=4.41 Hz, 3H), 2.89-2.94 (m, 4H), 5.28 (s, 2H), 6.80 (d, *J*=7.46 Hz, 1H), 7.17 (t, *J*=7.63 Hz, 1H), 7.25-7.27 (m, 1H), 7.31 (s, 1H), 7.36 (d, *J*=8.48 Hz, 2H), 7.44 (s, 1H), 7.59 (d, *J*=8.48 Hz, 2H), 7.65 (s, 1H), 7.80 (d, *J*=4.41 Hz, 1H), 8.65 (s, 1H), 8.84 (s, 1H); MS (ESI(+)) m/e 460 $(M+H)^+$.

Example 109

3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}propanamide

The desired product was prepared by substituting Example 100 for Example 14 in Example 15. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.29 (s, 3H), 2.50 (s, 2H), 2.92 (s, 2H), 5.26 (s, 2H), 6.79 (s, 2H), 7.21 (d, *J*=44.61 Hz, 2H), 7.34 (d, *J*=17.78 Hz, 4H), 7.43 (s, 1H), 7.60 (s, 2H), 7.68 (s, 1H), 8.76 (s, 1H), 8.96 (s, 1H); MS (ESI(+)) m/e 446 $(M+H)^+$.

Example 110

ethyl (2E)-3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}acrylate

The desired product was prepared by substituting Example 76B and ethyl acrylate for Example 10B and tert-butyl acrylate, respectively, in Example 11A, then substituting the product for Example 76B in Examples 76C-D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.29 (t, J=7.12 Hz, 3H), 2.29 (s, 3H), 4.22 (q, J=7.23 Hz, 2H), 6.05 (s, 2H), 6.39 (d, J=16.27 Hz, 1H), 6.81 (d, J=7.12 Hz, 1H), 7.17 (t, J=7.63 Hz, 1H), 7.23-7.27 (m, 1H), 7.32 (s, 1H), 7.39 (d, J=8.82 Hz, 2H), 7.61 (s, 2H), 7.63 (s, 1H), 7.81 (d, J=15.60 Hz, 1H), 8.27 (s, 1H), 8.67 (s, 1H), 8.88 (s, 1H); MS (ESI(+)) m/e 473 $(M+H)^+$.

Example 111

ethyl 3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}propanoate

The desired product was prepared by substituting Example 110 for Example 14 in Example 15. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.17 (t, J=7.12 Hz, 3H), 2.29 (s, 3H), 2.72 (t, J=7.46 Hz, 2H), 2.97 (t, J=7.29 Hz, 2H), 4.07 (q, J=7.12 Hz, 2H), 5.31 (s, 2H), 6.80 (d, J=7.12 Hz, 1H), 7.16 (t, J=7.63 Hz, 1H), 7.25 (d, J=8.14 Hz, 1H), 7.31 (s, 1H), 7.36 (d, J=8.48 Hz, 2H), 7.44 (s, 1H), 7.59 (d, J=8.48 Hz, 2H), 7.69 (s, 1H), 8.69 (s, 1H), 8.88 (s, 1H); MS (ESI(+)) m/e 475 $(M+H)^+$.

Example 112

(2E)-3-[4-amino-3-(4-aminophenyl)thieno[3,2-c]pyridin-7-yl]-N-methylacrylamide

Example 112A

(2E)-3-[4-amino-3-(4-aminophenyl)thieno[3,2-c]pyridin-7-yl]acrylic acid

The desired product was prepared by substituting Example 77A for Example 10B in Examples 11A-B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.44-5.48 (br s, 2H), 6.55 (d, J=16.27 Hz, 1H), 6.78 (d, J=8.48 Hz, 2H), 7.03 (s, 3H), 7.20 (d, J=8.48 Hz, 2H), 7.72-7.77 (m, 2H), 8.33 (s, 1H); MS (ESI(+)) m/e 312 $(M+H)^+$.

Example 112B

(2E)-3-[4-amino-3-(4-aminophenyl)thieno[3,2-c]pyridin-7-yl]-N-methylacrylamide

The desired product was prepared by substituting methylamine, Example 112A, and TBTU for 2-piperazinone, Example 11B, and HOBT, respectively, in Example 11C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.72 (s, 3H), 5.39 (s, 2H), 5.92 (s, 2H), 6.55 (d, J=15.94 Hz, 1H), 6.68 (d, J=8.48 Hz, 2H), 7.10 (d, J=8.48 Hz, 2H), 7.47 (s, 1H), 7.56 (d, J=15.94 Hz, 1H), 8.08 (s, 1H), 8.14 (q, J=4.18 Hz, 1H); MS (ESI(+)) m/e 325 $(M+H)^+$.

Example 113

N-(4-{4-amino-7-[(1E)-3-(methylamino)-3-oxo-1-propenyl]thieno[3,2-c]pyridin-3-yl}phenyl)-3-methylbenzamide

The desired product was prepared by substituting 3-methylbenzoyl chloride and Example 112 for acetyl chloride and Example 17A, respectively, in Example 17B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.42 (s, 3H), 2.74 (d, J=4.41 Hz, 3H), 5.86 (s, 2H), 6.58 (d, J=15.60 Hz, 1H), 7.44 (d, J=5.43 Hz, 2H), 7.48 (d, J=8.48 Hz, 2H), 7.59 (d, J=15.94 Hz, 1H), 7.66 (s, 1H), 7.80 (s, 2H), 7.95 (d, J=8.14 Hz, 2H), 8.13 (s, 1H), 8.16 (d, J=4.75 Hz, 1H), 10.41 (s, 1H); MS (ESI(+)) m/e 443 $(M+H)^+$.

Example 114

(2E)-3-[4-amino-3-(4-{[(3-methylphenyl)sulfonyl]amino}phenyl)thieno[3,2-c]pyridin-7-yl]-N-methylacrylamide

A solution of 3-methylbenzenesulfonyl chloride (70mg, 0.37 mmol) in DMF (1 mL) was added dropwise to a -30 °C solution of Example 112 (0.117g, 0.36 mmol) and N-methylmorpholine (0.057 mL, 0.54 mmol) in DMF (3 mL). The resulting mixture was stirred at -30 °C for 30 minutes, warmed to room temperature over 1.5 hours, and partitioned between water and ethyl acetate. The aqueous phase was extracted with ethyl acetate two times. The combined organics were dried (Na_2SO_4), filtered, concentrated and the residue was purified by flash column chromatography on silica gel with 5% methanol/dichloromethane to provide 55 mg (32% yield) of the desired product. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.37 (s, 3H), 2.72 (d, J=4.75 Hz, 3H), 5.73 (s, 2H), 6.56 (d, J=15.94 Hz, 1H), 7.22 (d, J=8.82 Hz, 2H), 7.36 (d, J=8.48 Hz, 2H), 7.46 (d, J=5.43 Hz, 2H), 7.58 (s, 2H), 7.64 (s, 2H), 8.10 (s, 1H), 8.14 (d, J=5.09 Hz, 1H), 10.50 (s, 1H); MS (ESI(+)) m/e 479 $(M+H)^+$.

Example 115

N-(4-{4-amino-7-[(1E)-3-(methylamino)-3-oxo-1-propenyl]thieno[3,2-c]pyridin-3-yl}phenyl)benzamide

The desired product was prepared by substituting benzoyl chloride and Example 112 for acetyl chloride and Example 17A, respectively, in Example 17B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.74 (d, J=4.75 Hz, 3H), 5.87 (s, 2H), 6.58 (d, J=15.93 Hz, 1H), 7.48-7.50 (m, 2H), 7.56 (s, 1H), 7.60-7.62 (m, 3H), 7.66 (s, 1H), 7.95 (s, 1H), 7.99-8.0 (m, 3H), 8.13 (s, 1H), 8.16 (d, J=4.75 Hz, 1H), 10.46 (s, 1H); MS (ESI(+)) m/e 429 $(M+H)^+$.

Example 116

(2E)-3-(4-amino-3-phenylthieno[3,2-c]pyridin-7-yl)-N,N-dimethylacrylamide

The desired product was prepared by substituting dimethylamine for methylamine

hydrochloride in Example 14. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.97 (s, 3H), 3.19 (s, 3H), 5.83 (s, 2H), 7.03 (d, *J*=15.60 Hz, 1H), 7.52-7.57 (m, 5H), 7.64-7.68 (m, 2H), 8.26 (s, 1H); MS (ESI(+)) m/e 324 $(M+H)^+$.

Example 117

(2E)-3-[4-amino-3-(4-aminophenyl)thieno[3,2-c]pyridin-7-yl]-N-[4-(dimethylamino)butyl]acrylamide

The desired product was prepared by substituting N,N-dimethyl-1,4-butanediamine, Example 112A, and TBTU for 2-piperazinone, Example 11B, and HOBT, respectively, in Example 11C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.10 (s, 6H), 2.83 (s, 4H), 3.40 (s, 4H), 5.40 (s, 2H), 5.94 (s, 2H), 6.57 (d, *J*=15.94 Hz, 1H), 6.68 (d, *J*=8.48 Hz, 2H), 7.10 (d, *J*=8.48 Hz, 2H), 7.48 (s, 1H), 7.59 (d, *J*=15.94 Hz, 1H), 8.09 (s, 1H), 8.34 (s, 1H); MS (ESI(+)) m/e 410 $(M+H)^+$.

Example 118

(2E)-3-[4-amino-3-(4-aminophenyl)thieno[3,2-c]pyridin-7-yl]-N-(3-pyridinylmethyl)acrylamide

The desired product was prepared by substituting 1-(3-pyridinyl)methanamine, Example 112A, and TBTU for 2-piperazinone, Example 11B, and HOBT, respectively, in Example 11C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.33 (s, 2H), 4.46 (d, *J*=5.76 Hz, 2H), 6.30 (s, 2H), 6.68 (d, *J*=5.42 Hz, 1H), 6.72 (d, *J*=2.03 Hz, 2H), 7.13 (d, *J*=8.48 Hz, 2H), 7.41 (dd, *J*=7.46, 4.41 Hz, 1H), 7.59 (s, 1H), 7.63 (d, *J*=15.93 Hz, 1H), 7.77-7.80 (m, 1H), 8.14 (s, 1H), 8.50 (dd, *J*=4.75, 1.70 Hz, 1H), 8.57 (d, *J*=1.36 Hz, 1H), 8.84 (t, *J*=5.76 Hz, 1H); MS (ESI(+)) m/e 402 $(M+H)^+$.

Example 119

3-(4-aminophenyl)-7-[(1E)-3-oxo-3-(1-piperazinyl)-1-propenyl]thieno[3,2-c]pyridin-4-amine

The desired product was prepared as the bis-trifluoroacetate salt by substituting tert-butyl 1-piperazinecarboxylate and Example 112A for piperazin-2-one and Example 11B, respectively, in Example 11C, then by removing the protecting group following the procedure of Example 11B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.85 (s, 8H), 4.24 (s, 2H), 6.76 (d, *J*=8.48 Hz, 2H), 6.98 (s, 1H), 7.18 (d, *J*=8.48 Hz, 2H), 7.26 (d, *J*=15.60 Hz, 1H), 7.66 (d, *J*=15.60 Hz, 1H), 7.74 (s, 1H), 8.38 (s, 1H), 8.92 (s, 2H); MS (ESI(+)) m/e 380 $(M+H)^+$.

Example 120

3-[4-amino-3-(4-aminophenyl)thieno[3,2-c]pyridin-7-yl]propanoic acid

The desired product was prepared by substituting Example 112A for Example 14 in

Example 15. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.72 (d, J=6.78 Hz, 4H), 2.89-2.99 (m, 2H), 6.71 (d, J=7.80 Hz, 2H), 6.97 (s, 2H), 7.15 (d, J=7.80 Hz, 2H), 7.73 (d, J=6.10 Hz, 2H), 12.36 (s, 1H); MS (ESI(+)) m/e 314 $(M+H)^+$.

Example 121

3-(4-aminophenyl)-7-(4-pyridinyl)thieno[3,2-c]pyridin-4-amine

Example 121A

tert-butyl 4-[4-amino-7-(4-pyridinyl)thieno[3,2-c]pyridin-3-yl]phenylcarbamate

A mixture of Example 77A (1.559g, 3.34 mmol), 4-pyridylboronic acid (0.431g, 3.51 mmol) and Na_2CO_3 (0.37g, 3.51 mmol) in THF/methanol/water (12 mL:2.4 mL:4 mL) was degassed by bubbling nitrogen through the solution for 15 minutes, then treated with Pd(dppf)Cl_2 (136mg, 0.17 mmol). The reaction vessel was sealed and heated to 90 °C for 17 hours. The reaction was cooled to room temperature and partitioned between water and ethyl acetate. The aqueous phase was extracted twice with ethyl acetate. The combined extracts were dried (Na_2SO_4), filtered, concentrated, and the residue was purified by flash column chromatography on silica gel with 3% methanol/dichloromethane to provide 0.65g (46%) of the desired product. MS (ESI(+)) m/e 419 $(M+H)^+$.

Example 121B

3-(4-aminophenyl)-7-(4-pyridinyl)thieno[3,2-c]pyridin-4-amine

A solution of Example 121A (0.11g, 0.263 mmol) in TFA (3 mL) and dichloromethane (1 mL) was stirred at room temperature for 30 minutes and concentrated under a stream of nitrogen. The residue was triturated from ethyl acetate/hexanes to provide 108 mg of the desired product. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.66 (s, 2H), 6.78 (d, J=8.14 Hz, 2H), 6.97 (s, 2H), 7.20 (d, J=8.48 Hz, 2H), 7.75 (s, 1H), 7.91 (d, J=6.44 Hz, 2H), 8.19 (s, 1H), 8.83 (d, J=6.44 Hz, 2H); MS (ESI(+)) m/e 319 $(M+H)^+$.

Example 122

N-{4-[4-amino-7-(4-pyridinyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea

A -20 °C solution of Example 121B (0.18g, 0.57 mmol) in DMF (3 mL) and THF (3 mL) was treated dropwise with 1-fluoro-2-isocyanato-4-(trifluoromethyl)benzene (0.085 mL, 0.57 mmol) and warmed to room temperature over 1.5 hours. The resulting mixture was diluted with water and extracted twice with ethyl acetate. The combined extracts were dried (Na_2SO_4), filtered, concentrated and the residue was purified by flash column chromatography on silica gel with 3-5% methanol/dichloromethane to provide 138 mg of the

desired product. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.74 (s, 2H), 7.44 (d, J=8.48 Hz, 3H), 7.51 (d, J=10.85 Hz, 1H), 7.55 (s, 1H), 7.64 (d, J=8.82 Hz, 2H), 7.71-7.72 (m, 1H), 7.74 (d, J=1.70 Hz, 1H), 8.10 (s, 1H), 8.64 (dd, J=7.29, 2.20 Hz, 1H), 8.67-8.69 (m, 1H), 8.70 (d, J=1.70 Hz, 1H), 8.98 (d, J=2.71 Hz, 1H), 9.40 (s, 1H); MS (ESI(+)) m/e 524 $(M+H)^+$.

Example 123

N-{4-[4-amino-7-(4-pyridinyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(2-fluoro-5-methylphenyl)urea

The desired product was prepared by substituting 1-fluoro-2-isocyanato-4-methylbenzene for 1-fluoro-2-isocyanato-4-(trifluoromethyl)benzene in Example 122. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 5.74 (s, 2H), 6.80-6.85 (m, 1H), 7.12 (dd, J=11.36, 8.31 Hz, 1H), 7.42 (d, J=8.82 Hz, 2H), 7.54 (s, 1H), 7.62 (d, J=8.48 Hz, 2H), 7.73-7.75 (m, 2H), 8.00 (dd, J=7.80, 2.03 Hz, 1H), 8.09 (s, 1H), 8.56 (d, J=2.71 Hz, 1H), 8.65-8.68 (m, 1H), 8.69 (d, J=1.70 Hz, 1H), 9.28 (s, 1H); MS (ESI(+)) m/e 470 $(M+H)^+$.

Example 124

3-(4-aminophenyl)-7-(3-pyridinyl)thieno[3,2-c]pyridin-4-amine

The desired product was prepared by substituting 3-pyridylboronic acid for 4-pyridylboronic acid in Examples 121A-B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.39 (s, 2H), 5.69 (s, 2H), 6.69 (d, J=8.48 Hz, 2H), 7.11 (d, J=8.14 Hz, 2H), 7.36 (s, 1H), 7.54 (dd, J=7.80, 4.75 Hz, 1H), 7.92 (s, 1H), 8.08 (d, J=7.80 Hz, 1H), 8.61 (d, J=4.07 Hz, 1H), 8.86 (s, 1H); MS (ESI(+)) m/e 319 $(M+H)^+$.

Example 125

N-{4-[4-amino-7-(3-pyridinyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(3-methylphenyl)urea

The desired product was prepared by substituting 1-isocyanato-3-methylbenzene and Example 124 for 1-fluoro-2-isocyanato-4-(trifluoromethyl)benzene and Example 121B, respectively, in Example 122. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 5.64 (s, 2H), 6.81 (d, J=7.46 Hz, 1H), 7.17 (t, J=7.80 Hz, 1H), 7.26-7.27 (m, 1H), 7.32 (s, 1H), 7.41 (d, J=8.82 Hz, 2H), 7.51 (s, 1H), 7.56 (dd, J=8.14, 4.75 Hz, 1H), 7.62 (d, J=8.82 Hz, 2H), 7.96 (s, 1H), 8.10-8.13 (m, 1H), 8.62 (dd, J=4.75, 1.70 Hz, 1H), 8.67 (s, 1H), 8.87 (s, 1H), 8.88 (s, 1H); MS (ESI(+)) m/e 452 $(M+H)^+$.

Example 126

3-(4-aminophenyl)-7-(3-thienyl)thieno[3,2-c]pyridin-4-amine

The desired product was prepared by substituting Example 77B and 3-thienylboronic acid for Example 77A and 4-pyridylboronic acid, respectively, in Example 121A. ^{1}H NMR

(300 MHz, DMSO-d_6) δ 5.37 (s, 2H), 5.59 (s, 2H), 6.68 (d, J=8.48 Hz, 2H), 7.11 (d, J=8.48 Hz, 2H), 7.36 (s, 1H), 7.55 (dd, J=5.09, 1.36 Hz, 1H), 7.72-7.73 (m, 1H), 7.78-7.79 (m, 1H), 8.05 (s, 1H); MS (ESI(+)) m/e 324 $(M+H)^+$.

Example 127

N-{4-[4-amino-7-(3-thienyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(3-methylphenyl)urea

The desired product was prepared by substituting for 1-isocyanato-3-methylbenzene and Example 126 for 1-fluoro-2-isocyanato-4-(trifluoromethyl)benzene and Example 121B, respectively, in Example 122. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 5.53 (s, 2H), 6.81 (d, J=7.46 Hz, 1H), 7.17 (t, J=7.80 Hz, 1H), 7.26-7.28 (m, 1H), 7.32 (s, 1H), 7.40 (d, J=8.81 Hz, 2H), 7.51 (s, 1H), 7.57 (dd, J=5.09, 1.36 Hz, 1H), 7.61 (d, J=8.81 Hz, 2H), 7.73 (dd, J=4.92, 2.88 Hz, 1H), 7.80-7.83 (m, 1H), 8.09 (s, 1H), 8.66 (s, 1H), 8.86 (s, 1H); MS (ESI(-)) m/e 455 $(M-H)^-$.

Example 128

N-{4-[4-amino-7-(6-methoxy-3-pyridinyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea

Example 128A

3-(4-aminophenyl)-7-(6-methoxy-3-pyridinyl)thieno[3,2-c]pyridin-4-amine

The desired product was prepared by substituting Example 77B and 6-methoxy-3-pyridinylboronic acid for Example 77A and 4-pyridylboronic acid, respectively, in Example 121A. MS (ESI(+)) m/e 349 $(M+H)^+$.

Example 128B

N-{4-[4-amino-7-(6-methoxy-3-pyridinyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea

The desired product was prepared by substituting Example 128A for Example 121B in Example 122. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.93 (s, 3H), 5.55 (s, 2H), 6.99 (d, J=8.48 Hz, 1H), 7.39-7.45 (m, 3H), 7.49-7.55 (m, 2H), 7.64 (d, J=8.48 Hz, 2H), 7.89 (s, 1H), 8.00 (dd, J=8.65, 2.54 Hz, 1H), 8.45 (d, J=2.37 Hz, 1H), 8.64 (dd, J=7.46, 2.03 Hz, 1H), 8.98 (d, J=2.71 Hz, 1H), 9.39 (s, 1H); MS (ESI(+)) m/e 554 $(M+H)^+$.

Example 129

N-{4-[4-amino-7-(6-methoxy-3-pyridinyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(2-fluoro-5-methylphenyl)urea

The desired product was prepared by substituting for 1-fluoro-2-isocyanato-4-

methylbenzene and Example 128A for 1-fluoro-2-isocyanato-4-(trifluoromethyl)benzene and Example 121B, respectively, in Example 122. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 3.93 (s, 3H), 5.55 (s, 2H), 6.82-6.84 (m, 1H), 6.97-7.00 (m, 1H), 7.12 (dd, *J*=11.53, 8.48 Hz, 1H), 7.41 (d, *J*=8.48 Hz, 2H), 7.50 (s, 1H), 7.62 (d, *J*=8.48 Hz, 2H), 7.88 (s, 1H), 8.00-8.03 (m, 2H), 8.44 (d, *J*=2.37 Hz, 1H), 8.56 (d, *J*=2.37 Hz, 1H), 9.27 (s, 1H); MS (ESI(+)) m/e 500 $(M+H)^+$.

Example 130

N-{4-[4-amino-7-(6-methoxy-3-pyridinyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-[3-(trifluoromethyl)phenyl]urea

The desired product was prepared by substituting for 1-isocyanato-3-(trifluoromethyl)benzene and Example 128A for 1-fluoro-2-isocyanato-4-(trifluoromethyl)benzene and Example 121B, respectively, in Example 122. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.93 (s, 3H), 5.56 (s, 2H), 6.99 (d, *J*=8.48 Hz, 1H), 7.33 (d, *J*=7.46 Hz, 1H), 7.42 (d, *J*=8.48 Hz, 2H), 7.50 (s, 1H), 7.55 (d, *J*=7.46 Hz, 1H), 7.60 (s, 1H), 7.64 (d, *J*=8.48 Hz, 2H), 7.89 (s, 1H), 8.00 (dd, *J*=8.48, 2.71 Hz, 1H), 8.04 (s, 1H), 8.44 (d, *J*=2.37 Hz, 1H), 9.02 (s, 1H), 9.13 (s, 1H); MS (ESI(+)) m/e 534 $(M+H)^+$.

Example 131

N-{4-[4-amino-7-(4-cyanophenyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea

Example 131A

4-[4-Amino-3-(4-amino-phenyl)-thieno[3,2-c]pyridin-7-yl]-benzonitrile

The desired product was prepared by substituting Example 77B and 4-cyanophenylboronic acid for Example 77A and 4-pyridylboronic acid, respectively, in Example 121A. MS (ESI(+)) m/e 343 $(M+H)^+$.

Example 131B

N-{4-[4-amino-7-(4-cyanophenyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea

The desired product was prepared by substituting Example 131A for Example 121B in Example 122. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.71 (s, 2H), 7.40-7.45 (m, 3H), 7.51 (d, *J*=10.85 Hz, 1H), 7.54 (s, 1H), 7.64 (d, *J*=8.81 Hz, 2H), 7.90 (d, *J*=8.81 Hz, 2H), 7.96-8.00 (m, 2H), 8.02 (s, 1H), 8.64 (dd, *J*=7.46, 2.37 Hz, 1H), 8.98 (d, *J*=3.05 Hz, 1H), 9.39 (s, 1H); MS (ESI(+)) m/e 548 $(M+H)^+$.

Example 132

N-{4-[4-amino-7-(4-cyanophenyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(2-fluoro-5-methylphenyl)urea

The desired product was prepared by substituting for 1-fluoro-2-isocyanato-4-methylbenzene and Example 131A for 1-fluoro-2-isocyanato-4-(trifluoromethyl)benzene and Example 121B, respectively, in Example 122. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.31 (s, 3H), 5.71 (s, 2H), 6.79-6.84 (m, 1H), 7.12 (dd, *J*=11.36, 8.31 Hz, 1H), 7.42 (d, *J*=8.48 Hz, 2H), 7.53 (s, 1H), 7.62 (d, *J*=8.48 Hz, 2H), 7.90 (d, *J*=8.48 Hz, 2H), 7.97-8.03 (m, 4H), 8.56 (d, *J*=2.37 Hz, 1H), 9.28 (s, 1H); MS (ESI(+)) m/e 494 $(M+H)^+$.

Example 133

N-{4-[4-amino-7-(2-methoxy-5-pyrimidinyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea

Example 133A

3-(4-aminophenyl)-7-(2-methoxy-5-pyrimidinyl)thieno[3,2-c]pyridin-4-amine

The desired product was prepared by substituting 2-methoxy-5-pyrimidinylboronic acid for 4-pyridylboronic acid in Examples 121A-B. MS (ESI(+)) m/e 350 $(M+H)^+$.

Example 133B

N-{4-[4-amino-7-(2-methoxy-5-pyrimidinyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea

The desired product was prepared by substituting Example 131A for Example 121B in Example 122. ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.00 (s, 3H), 5.64 (s, 2H), 7.43 (d, *J*=8.48 Hz, 3H), 7.49-7.55 (m, 2H), 7.64 (d, *J*=8.48 Hz, 2H), 7.95 (s, 1H), 8.63-8.66 (m, 1H), 8.90 (s, 2H), 8.98 (d, *J*=2.37 Hz, 1H), 9.39 (s, 1H); MS (ESI(+)) m/e 555 $(M+H)^+$.

Example 134

N-{4-[4-amino-7-(2-methoxy-5-pyrimidinyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-[3-(trifluoromethyl)phenyl]urea

The desired product was prepared by substituting 1-isocyanato-3-(trifluoromethyl)benzene and Example 131A for 1-fluoro-2-isocyanato-4-(trifluoromethyl)benzene and Example 121B, respectively, in Example 122. ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.00 (s, 3H), 5.65 (s, 2H), 7.33 (d, *J*=7.80 Hz, 1H), 7.42 (d, *J*=8.48 Hz, 2H), 7.51-7.56 (m, 2H), 7.61 (d, *J*=8.48 Hz, 2H), 7.65 (s, 1H), 7.94 (s, 1H), 8.04 (s, 1H), 8.90 (s, 2H), 9.03 (s, 1H), 9.13 (s, 1H); MS (ESI(+)) m/e 537 $(M+H)^+$.

Example 135

N-{4-[4-amino-7-(2,6-dimethyl-3-pyridinyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea

Example 135A

3-(4-aminophenyl)-7-(2,6-dimethyl-3-pyridinyl)thieno[3,2-c]pyridin-4-amine

The desired product was prepared by substituting 2,6-dimethyl-3-pyridinylboronic acid for 4-pyridylboronic acid in Examples 121A-B. MS (ESI(+)) m/e 347 $(M+H)^+$.

Example 135B

N-{4-[4-amino-7-(2,6-dimethyl-3-pyridinyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea

The desired product was prepared by substituting Example 135A for Example 121B in Example 122. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.31 (s, 3H), 2.32 (s, 3H), 5.54 (s, 2H), 6.68 (d, J=8.48 Hz, 1H), 7.12 (d, J=8.48 Hz, 1H), 7.17-7.21 (m, 2H), 7.40-7.49 (m, 3H), 7.57-7.67 (m, 2H), 7.72 (s, 1H), 8.64 (dd, J=7.46, 2.03 Hz, 1H), 8.98 (d, J=2.71 Hz, 1H), 9.38 (s, 1H); MS (ESI(+)) m/e 552 $(M+H)^+$.

Example 136

N-{4-[4-amino-7-(5-pyrimidinyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(3-methylphenyl)urea

Example 136A

3-(4-aminophenyl)-7-(5-pyrimidinyl)thieno[3,2-c]pyridin-4-amine

The desired product was prepared by substituting 5-pyrimidinylboronic acid for 4-pyridylboronic acid in Examples 121A-B. MS (ESI(+)) m/e 320 $(M+H)^+$.

Example 136B

N-{4-[4-amino-7-(5-pyrimidinyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(3-methylphenyl)urea

The desired product was prepared by substituting 1-isocyanato-3-methylbenzene and Example 136A for 1-fluoro-2-isocyanato-4-(trifluoromethyl)benzene and Example 121B, respectively, in Example 122. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 5.75 (d, J=2.71 Hz, 2H), 6.81 (d, J=7.46 Hz, 1H), 7.17 (t, J=7.80 Hz, 1H), 7.26-7.28 (m, 1H), 7.32 (s, 1H), 7.40 (d, J=8.48 Hz, 2H), 7.54 (s, 1H), 7.62 (d, J=8.48 Hz, 2H), 8.04 (s, 1H), 8.67 (s, 1H), 8.88 (s, 1H), 9.14 (s, 2H), 9.23 (s, 1H); MS (ESI(+)) m/e 453 $(M+H)^+$.

Example 137

N-{4-[4-amino-7-(5-pyrimidinyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-[2-fluoro-5-

(trifluoromethyl)phenyl]urea

The desired product was prepared by substituting Example 136A for Example 121B in Example 122. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.74 (s, 2H), 7.44 (d, J=8.48 Hz, 3H), 7.49-7.56 (m, 2H), 7.65 (d, J=8.48 Hz, 2H), 8.05 (s, 1H), 8.65 (d, J=7.12 Hz, 1H), 8.98 (d, J=2.37 Hz, 1H), 9.14 (s, 2H), 9.24 (s, 1H), 9.40 (s, 1H); MS (ESI(+)) m/e 525 $(M+H)^+$.

Example 138

3-(4-aminophenyl)-7-[4-(benzyloxy)phenyl]thieno[3,2-c]pyridin-4-amine

The desired product was prepared by substituting Example 77B and 4-benzyloxyphenylboronic acid for Example 77A and 4-pyridylboronic acid, respectively, in Example 121A. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.18 (s, 2H), 5.37 (s, 2H), 5.53 (s, 2H), 6.68 (d, J=8.14 Hz, 2H), 7.10 (d, J=8.14 Hz, 2H), 7.15 (d, J=8.82 Hz, 2H), 7.32 (s, 1H), 7.48-7.51 (m, 3H), 7.53-7.55 (m, 2H), 7.57 (d, J=8.82 Hz, 2H), 7.81 (s, 1H); MS (ESI(+)) m/e 424 $(M+H)^+$.

Example 139

4-[4-amino-3-(4-aminophenyl)thieno[3,2-c]pyridin-7-yl]phenol

A suspension of Example 138 (132 mg) in 48% HBr (2 mL) and acetic acid (4 mL) was heated to 80 °C for 3 hours. The resulting homogeneous solution was concentrated and the residue was triturated from ethanol/diethyl ether to provide 130 mg of the desired product the dihydrobromide salt. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.67 (s, 2H), 6.95-6.98 (m, 6H), 7.34 (d, J=8.48 Hz, 2H), 7.51 (d, J=8.82 Hz, 2H), 7.85 (d, J=8.82 Hz, 2H), 9.83 (s, 1H); MS (ESI(+)) m/e 334 $(M+H)^+$.

Example 140

N-{4-[4-amino-7-(4-hydroxyphenyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(3-methylphenyl)urea

The desired product was prepared as the hydrobromide salt by substituting Example 138 for Example 1C in Example 1D, then substituting the product for Example 138 in Example 139. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 6.82 (d, J=7.12 Hz, 1H), 6.90 (s, 2H), 6.96-6.99 (m, 2H), 7.18 (t, J=7.80 Hz, 1H), 7.27 (d, J=8.48 Hz, 1H), 7.32 (s, 1H), 7.46 (d, J=8.48 Hz, 2H), 7.52-7.55 (m, 2H), 7.67 (d, J=8.48 Hz, 2H), 7.89 (d, J=4.07 Hz, 2H), 8.75 (s, 1H), 9.02 (s, 1H), 9.88 (s, 1H); MS (ESI(+)) m/e 467 $(M+H)^+$.

Example 141

3-{4-amino-3-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-c]pyridin-7-yl}-N-methylbenzamide

The desired product was prepared as the trifluoroacetate salt by substituting 3-[(methylamino)carbonyl]phenylboronic acid for 4-pyridylboronic acid in Examples 121A-B, then substituting the product and 1-isocyanato-3-methylbenzene for Example 121B and 1-fluoro-2-isocyanato-4-(trifluoromethyl)benzene, respectively, in Example 122. The product was purified by HPLC as described in Example 82. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.09 (s, 3H), 2.29 (s, 3H), 6.82 (d, *J*=7.46 Hz, 1H), 6.96 (s, 2H), 7.18 (t, *J*=7.80 Hz, 1H), 7.27-7.29 (m, 1H), 7.34-7.36 (m, 2H), 7.47 (d, *J*=8.82 Hz, 2H), 7.53-7.55 (m, 1H), 7.61-7.63 (m, 1H), 7.67 (d, *J*=8.48 Hz, 2H), 7.88 (s, 1H), 7.95 (s, 1H), 8.12 (s, 1H), 8.83 (s, 1H), 9.09 (s, 1H), 10.19 (s, 1H); MS (ESI(+)) m/e 508 $(M+H)^+$.

Example 142

N-[4-(4-amino-7-phenylthieno[3,2-c]pyridin-3-yl)phenyl]-N'-(3-methylphenyl)urea

The desired product was prepared by substituting phenylboronic acid for 4-pyridylboronic acid in Examples 121A-B, then substituting the product and 1-isocyanato-3-methylbenzene for Example 121B and 1-fluoro-2-isocyanato-4-(trifluoromethyl)benzene, respectively, in Example 122. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 5.54 (s, 2H), 6.81 (d, *J*=7.46 Hz, 1H), 7.17 (t, *J*=7.63 Hz, 1H), 7.26-7.28 (m, 1H), 7.32 (s, 1H), 7.40 (d, *J*=8.14 Hz, 2H), 7.48-7.55 (m, 4H), 7.61 (d, *J*=8.48 Hz, 2H), 7.67 (d, *J*=7.12 Hz, 2H), 7.91 (s, 1H), 8.67 (s, 1H), 8.86 (s, 1H); MS (ESI(+)) m/e 451 $(M+H)^+$.

Example 143

N-{4-[4-amino-7-(4-pyridinyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(3-methylphenyl)urea

The desired product was prepared by substituting 1-isocyanato-3-methylbenzene for 1-fluoro-2-isocyanato-4-(trifluoromethyl)benzene in Example 122. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 5.74 (s, 2H), 6.81 (d, *J*=7.46 Hz, 1H), 7.17 (t, *J*=7.80 Hz, 1H), 7.26-7.27 (m, 1H), 7.32 (s, 1H), 7.40 (d, *J*=8.81 Hz, 2H), 7.53 (s, 1H), 7.62 (d, *J*=8.48 Hz, 2H), 7.72-7.73 (m, 1H), 7.73 (d, *J*=1.70 Hz, 1H), 8.09 (s, 1H), 8.67 (t, *J*=2.20 Hz, 2H), 8.69 (d, *J*=1.36 Hz, 1H), 8.87 (s, 1H); MS (ESI(+)) m/e 452 $(M+H)^+$.

Example 144

N-{4-[4-amino-7-(4-hydroxy-1-butynyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(3-methylphenyl)urea

Example 144A

N-[4-(4-amino-7-iodothieno[3,2-c]pyridin-3-yl)phenyl]-N'-(3-methylphenyl)urea

The desired product was prepared by substituting Example 77B for Example 1C in Example 1D. MS (ESI(+)) m/e 501 $(M+H)^+$.

Example 144B

N-{4-[4-amino-7-(4-hydroxy-1-butynyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(3-methylphenyl)urea

A suspension of Example 144A (0.227g, 0.45 mmol) in piperidine (3 mL) was degassed by bubbling nitrogen through the suspension for 5 minutes, treated with 3-butyn-1-ol (0.069 mL, 0.91 mmol), $Pd(PPh_3)_4$ (26mg, 0.023 mmol), and CuI (5mg, 0.023 mmol), then heated to 80 °C in a sealed tube for 30 minutes. The resulting homogeneous solution was cooled to room temperature and concentrated under a stream of nitrogen. The residue was purified by flash column chromatography on silica gel with 5% methanol/dichloromethane to provide 164 mg (81%) of the desired product. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 2.65 (t, *J*=6.78 Hz, 2H), 3.63 (q, *J*=6.73 Hz, 2H), 4.92 (t, *J*=5.59 Hz, 1H), 5.70 (s, 2H), 6.81 (d, *J*=7.46 Hz, 1H), 7.17 (t, *J*=7.80 Hz, 1H), 7.25-7.28 (m, 1H), 7.32 (s, 1H), 7.37 (d, *J*=8.48 Hz, 2H), 7.49 (s, 1H), 7.60 (d, *J*=8.48 Hz, 2H), 7.93 (s, 1H), 8.65 (s, 1H), 8.85 (s, 1H); MS (ESI(+)) m/e 443 $(M+H)^+$.

Examples 145-156 were prepared by substituting the appropriate alkyne (X) for 3-butyn-1-ol in Example 144B.

Example 145

N-{4-[4-amino-7-(3-phenoxy-1-propynyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(3-methylphenyl)urea

X = (2-propynyloxy)benzene. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 5.14 (s, 2H), 5.85 (s, 2H), 6.80 (d, *J*=7.46 Hz, 1H), 6.99 (t, *J*=7.29 Hz, 1H), 7.09 (d, *J*=7.46 Hz, 2H), 7.16 (t, *J*=7.80 Hz, 1H), 7.25-7.27 (m, 1H), 7.31-7.38 (m, 5H), 7.51 (s, 1H), 7.60 (d, *J*=8.48 Hz, 2H), 8.00 (s, 1H), 8.65 (s, 1H), 8.85 (s, 1H); MS (ESI(+)) m/e 505 $(M+H)^+$.

Example 146

N-{4-[4-amino-7-(4-pyridinylethynyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(3-methylphenyl)urea

X= 4-ethynylpyridine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 6.00 (s, 2H), 6.81 (d, *J*=6.78 Hz, 1H), 7.17 (t, *J*=7.80 Hz, 1H), 7.24-7.27 (m, 1H), 7.32 (s, 1H), 7.40 (d, *J*=8.48 Hz, 2H), 7.53 (d, *J*=5.09 Hz, 2H), 7.59 (d, *J*=6.10 Hz, 2H), 7.63 (s, 1H), 8.18 (s, 1H), 8.66 (s, 3H), 8.87 (s, 1H); MS (ESI(+)) m/e 476 $(M+H)^+$.

Example 147

N-[4-(4-amino-7-{3-[benzyl(methyl)amino]-1-propynyl}thieno[3,2-c]pyridin-3-yl)phenyl]-

N'-(3-methylphenyl)urea

X = N-benzyl-N-methyl-N-2-propynylamine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 2.34 (s, 3H), 3.61 (s, 2H), 3.66 (s, 2H), 5.78 (s, 2H), 6.81 (d, *J*=7.46 Hz, 1H), 7.17 (t, *J*=7.63 Hz, 1H), 7.32-7.40 (m, 9H), 7.53 (s, 1H), 7.61 (d, *J*=8.81 Hz, 2H), 8.01 (s, 1H), 8.66 (s, 1H), 8.86 (s, 1H); MS (ESI(+)) m/e 532 $(M+H)^+$.

Example 148

N-{4-[4-amino-7-(3-hydroxy-1-propynyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(3-methylphenyl)urea

X= 2-propyn-1-ol. The product was prepared as the trifluoroacetate salt by HPLC purification using the conditions described in Example 82. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 4.41 (s, 2H), 6.54 (s, 2H), 6.81 (d, *J*=7.12 Hz, 1H), 7.17 (t, *J*=7.80 Hz, 1H), 7.26 (t, *J*=4.41 Hz, 2H), 7.32 (s, 1H), 7.41 (d, *J*=8.48 Hz, 2H), 7.63 (d, *J*=8.81 Hz, 2H), 7.71 (s, 1H), 8.06 (s, 1H), 8.78 (s, 1H), 9.01 (s, 1H); MS (ESI(+)) m/e 429 $(M+H)^+$.

Example 149

N-{4-[4-amino-7-(3-pyridinylethynyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(3-methylphenyl)urea

X = 3-ethynylpyridine. The product was prepared as the bis(trifluoroacetate) salt HPLC purification using the conditions described in Example 82. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 6.61 (s, 2H), 6.81 (d, *J*=7.46 Hz, 1H), 7.17 (t, *J*=7.63 Hz, 1H), 7.26-7.28 (m, 1H), 7.32 (s, 1H), 7.43 (d, *J*=8.81 Hz, 2H), 7.50-7.55 (m, 1H), 7.62-7.66(m, 2H), 7.75 (s, 1H), 8.04 (ddd, *J*=8.31, 1.86, 1.70 Hz, 1H), 8.24 (s, 1H), 8.64 (d, *J*=4.07 Hz, 1H), 8.76 (s, 1H), 8.82 (s, 1H), 8.99 (s, 1H); MS (ESI(+)) m/e 476 $(M+H)^+$.

Example 150

N-(4-{4-amino-7-[3-(phenylsulfanyl)-1-propynyl]thieno[3,2-c]pyridin-3-yl}phenyl)-N'-(3-methylphenyl)urea

X = (2-propynylsulfanyl)benzene. The product was prepared as the trifluoroacetate salt by HPLC purification using the conditions described in Example 82. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.29 (s, 3H), 4.24 (s, 2H), 6.80 (d, *J*=7.36 Hz, 2H), 7.17 (t, *J*=7.67 Hz, 1H), 7.27 (d, *J*=4.60 Hz, 2H), 7.34 (s, 1H), 7.38-7.41 (m, 5H), 7.53 (d, *J*=7.36 Hz, 2H), 7.65 (d, *J*=8.59 Hz, 2H), 7.73 (s, 1H), 8.01 (s, 1H), 8.94 (s, 1H), 9.18 (s, 1H); MS (ESI(+)) m/e 521 $(M+H)^+$.

Example 151

N-{4-[4-amino-7-(4-cyano-1-butynyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(3-

methylphenyl)urea

X = 4-pentynenitrile. The product was prepared as the trifluoroacetate salt by HPLC purification using the conditions described in Example 82. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 2.85-2.95 (m, 4H), 6.66 (s, 2H), 6.81 (d, *J*=7.46 Hz, 1H), 7.17 (t, *J*=7.63 Hz, 1H), 7.26-7.27 (m, 1H), 7.32 (s, 1H), 7.41 (d, *J*=8.48 Hz, 2H), 7.64 (d, *J*=8.48 Hz, 2H), 7.76 (s, 1H), 8.06 (s, 1H), 8.76 (s, 1H), 8.99 (s, 1H); MS (ESI(+)) m/e 452 $(M+H)^+$.

Example 152

N-{4-[4-amino-7-(1-pentynyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(3-methylphenyl)urea

X= 1-pentyne. The product was prepared as the trifluoroacetate salt by HPLC purification using the conditions described in Example 82. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.07 (t, *J*=7.29 Hz, 3H), 1.63 (m, 2H), 2.29 (s, 3H), 2.52-2.56 (m, 2H), 6.75 (s, 2H), 6.81 (d, *J*=7.46 Hz, 1H), 7.17 (t, *J*=7.63 Hz, 1H), 7.26-7.28 (m, 1H), 7.32 (s, 1H), 7.42 (d, *J*=8.48 Hz, 2H), 7.64 (d, *J*=8.48 Hz, 2H), 7.77 (s, 1H), 8.04 (s, 1H), 8.78 (s, 1H), 9.02 (s, 1H); MS (ESI(+)) m/e 441 $(M+H)^+$.

Example 153

N-(4-{4-amino-7-[3-(diethylamino)-1-propynyl]thieno[3,2-c]pyridin-3-yl}phenyl)-N'-(3-methylphenyl)urea

X = N,N-diethyl-N-2-propynylamine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.06 (t, *J*=7.12 Hz, 6H), 2.29 (s, 3H), 2.59 (q, *J*=7.12 Hz, 4H), 3.70 (s, 2H), 5.75 (s, 2H), 6.80 (d, *J*=7.46 Hz, 1H), 7.17 (t, *J*=7.63 Hz, 1H), 7.25-7.28 (m, 1H), 7.32 (s, 1H), 7.37 (d, *J*=8.48 Hz, 2H), 7.50 (s, 1H), 7.60 (d, *J*=8.48 Hz, 2H), 7.96 (s, 1H), 8.66 (s, 1H), 8.87 (s, 1H); MS (ESI(+)) m/e 484 $(M+H)^+$.

Example 154

N-{4-[4-amino-7-(4-phenyl-1-butynyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(3-methylphenyl)urea

X = 3-butynylbenzene. The product was prepared as the trifluoroacetate salt by HPLC purification using the conditions described in Example 82. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 2.83-2.96 (m, 4H), 6.67 (s, 2H), 6.81 (d, *J*=7.46 Hz, 1H), 7.17 (t, *J*=7.80 Hz, 1H), 7.25-7.28 (m, 2H), 7.34-7.38 (m, 5H), 7.40 (d, *J*=8.81 Hz, 2H), 7.64 (d, *J*=8.81 Hz, 2H), 7.75 (s, 1H), 7.98 (s, 1H), 8.78 (s, 1H), 9.02 (s, 1H); MS (ESI(-)) m/e 501 $(M-H)^-$.

Example 155

N-(4-{4-amino-7-[3-(methylamino)-1-propynyl]thieno[3,2-c]pyridin-3-yl}phenyl)-N'-(3-methylphenyl)urea

X = N-methyl-N-2-propynylamine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 2.41 (s, 3H), 3.39 (s, 1H), 3.60 (s, 2H), 5.74 (s, 2H), 6.81 (d, *J*=7.46 Hz, 1H), 7.17 (t, *J*=7.80 Hz, 1H), 7.24-7.27 (m, 1H), 7.32 (s, 1H), 7.38 (d, *J*=8.82 Hz, 2H), 7.50 (s, 1H), 7.60 (d, *J*=8.82 Hz, 2H), 7.95 (s, 1H), 8.69 (s, 1H), 8.89 (s, 1H); MS (ESI(+)) m/e 442 $(M+H)^+$.

Example 156

N-[4-(4-amino-7-{3-[(aminocarbonyl)amino]-1-propynyl}thieno[3,2-c]pyridin-3-yl)phenyl]-N'-(3-methylphenyl)urea

X = N-2-propynylurea. The product was prepared as the bis(trifluoroacetate) salt by HPLC purification using the conditions described in Example 82. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 4.14 (d, *J*=4.75 Hz, 2H), 5.67 (s, 2H), 6.45 (t, *J*=5.59 Hz, 1H), 6.71 (s, 2H), 6.81 (d, *J*=7.12 Hz, 1H), 7.17 (t, *J*=7.80 Hz, 1H), 7.24-7.27 (m, 1H), 7.32 (s, 1H), 7.42 (d, *J*=8.48 Hz, 2H), 7.64 (d, *J*=8.48 Hz, 2H), 7.77 (s, 1H), 8.06 (s, 1H), 8.78 (s, 1H), 9.02 (s, 1H); MS (ESI(+)) m/e 471 $(M+H)^+$.

Example 157

N-{4-[4-amino-7-(4-hydroxybutyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(3-methylphenyl)urea

The desired product was prepared by substituting Example 144B for Example 14 in Example 15. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.48-1.57 (m, 2H), 1.69-1.74 (m, 2H), 2.29 (s, 3H), 2.71 (t, *J*=7.29 Hz, 2H), 3.43-3.46 (m, 2H), 4.39 (t, *J*=5.09 Hz, 1H), 5.39 (s, 2H), 6.81 (d, *J*=7.12 Hz, 1H), 7.17 (t, *J*=7.63 Hz, 1H), 7.25-7.28 (m, 1H), 7.31 (s, 1H), 7.37 (d, *J*=8.48 Hz, 2H), 7.46 (s, 1H), 7.59 (d, *J*=8.48 Hz, 2H), 7.68 (s, 1H), 8.66 (s, 1H), 8.85 (s, 1H); MS (ESI(+)) m/e 447 $(M+H)^+$.

Example 158

3-(4-aminophenyl)-7-(4-isoquinolinyl)thieno[3,2-c]pyridin-4-amine

The desired product was prepared by substituting 4-isoquinolinylboronic acid for 4-pyridylboronic acid in Examples 121A-B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.40 (s, 2H), 5.75 (s, 2H), 6.70 (d, *J*=8.48 Hz, 2H), 7.14 (d, *J*=8.48 Hz, 2H), 7.39 (s, 1H), 7.65-7.70 (m, 1H), 7.81 (ddd, *J*=8.39, 6.87, 1.70 Hz, 1H), 8.09-8.11 (m, 3H), 8.63 (d, *J*=2.37 Hz, 1H), 9.21 (d, *J*=2.03 Hz, 1H). MS (ESI(+)) m/e 369 $(M+H)^+$.

Example 159

3-(4-aminophenyl)-7-(2,6-difluoro-3-pyridinyl)thieno[3,2-c]pyridin-4-amine

The desired product was prepared by substituting 2,6-difluoro-3-pyridinylboronic acid for 4-pyridylboronic acid in Examples 121A-B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.39 (s,

2H), 5.75 (s, 2H), 6.67-6.70 (m, 2H), 7.11 (d, J=8.48 Hz, 2H), 7.33-7.37 (m, 2H), 7.85 (s, 1H), 8.34-8.42 (m, 1H). MS (ESI(+)) m/e 355 $(M+H)^+$.

Example 160

3-(1H-indol-6-yl)thieno[3,2-c]pyridin-4-amine

The desired product was prepared by substituting 1H-indol-6-ylboronic acid for 4-phenoxyphenylboronic acid in Example 10A. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.41 (s, 2H), 6.52 (s, 1H), 7.05 (dd, J=8.14, 1.70 Hz, 1H), 7.26 (d, J=5.76 Hz, 1H), 7.45 (m, 3H), 7.67 (d, J=8.14 Hz, 1H), 7.82 (d, J=5.43 Hz, 1H), 11.29 (s, 1H); MS (ESI(+)) m/e 266 $(M+H)^+$.

Example 161

N-{4-[4-amino-7-(2,6-difluoro-3-pyridinyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(2-fluoro-5-methylphenyl)urea

The desired product was prepared by substituting Example 159 and 1-fluoro-2-isocyanato-4-methylbenzene for Example 121 and 1-fluoro-2-isocyanato-4-(trifluoromethyl)benzene, respectively, in Example 122. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.28 (s, 3H), 5.71 (s, 2H), 6.83 (dd, J=4.58, 2.20 Hz, 1H), 7.09-7.16 (m, 1H), 7.36 (dd, J=8.14, 2.37 Hz, 1H), 7.42 (d, J=8.48 Hz, 2H), 7.51 (s, 1H), 7.62 (d, J=8.48 Hz, 2H), 7.90 (s, 1H), 8.00 (dd, J=7.97, 1.87 Hz, 1H), 8.36-8.44 (m, 1H), 8.56 (d, J=2.37 Hz, 1H), 9.27 (s, 1H). MS (ESI(+)) m/e 506 $(M+H)^+$.

Example 162

N-{4-[4-amino-7-(2,6-difluoro-3-pyridinyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(3-methylphenyl)urea

The desired product was prepared by substituting Example 159 and 1-isocyanato-3-methylbenzene for Example 121 and 1-fluoro-2-isocyanato-4-(trfluoromethy)benzene, respectively, in Example 122. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 5.71 (s, 2H), 6.81 (d, J=7.46 Hz, 1H), 7.17 (t, J=7.63 Hz, 1H), 7.26-7.28 (m, 1H), 7.32 (s, 1H), 7.36-7.39 (m, 1H), 7.41 (d, J=8.81 Hz, 2H), 7.50 (s, 1H), 7.62 (d, J=8.48 Hz, 2H), 7.89 (s, 1H), 8.39-8.44 (m, 1H), 8.67 (s, 1H), 8.87 (s, 1H). MS (ESI(-)) m/e 486 $(M-H)^-$.

Example 163

N-{4-[4-amino-7-(4-isoquinolinyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea

The desired product was prepared by substituting Example 158 for Example 121 in Example 122. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.69 (s, 2H), 7.39-7.74 (m, 1H), 7.46 (d,

J=8.48 Hz, 2H), 7.51 (d, J=11.19 Hz, 1H), 7.56 (s, 1H), 7.64 (s, 1H), 7.67 (d, J=2.37 Hz, 1H), 7.70 (d, J=7.80 Hz, 1H), 7.79-7.84 (m, 1H), 8.08 (s, 1H), 8.11 (d, J=2.03 Hz, 1H), 8.12 (s, 1H), 8.64 (d, J=2.03 Hz, 1H), 8.65 (d, J=2.03 Hz, 1H), 8.98 (d, J=2.71 Hz, 1H), 9.22 (d, J=2.37 Hz, 1H), 9.40 (s, 1H). MS (ESI(-)) m/e 572 $(M-H)^-$.

Example 164

N-{4-[4-amino-7-(4-isoquinolinyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(3-methylphenyl)urea

The desired product was prepared by substituting Example 158 and 1-isocyanato-3-methylbenzene for Example 121 and 1-fluoro-2-isocyanato-4-(trfluoromethy)benzene, respectively, in Example 122. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30 (s, 3H), 5.70 (s, 2H), 6.81 (d, J=7.46 Hz, 1H), 7.18-7.21 (m, 1H), 7.27-7.29 (m, 1H), 7.33 (s, 1H), 7.43 (d, J=8.82 Hz, 2H), 7.54 (s, 1H), 7.63 (d, J=8.48 Hz, 2H), 7.70 (d, J=7.80 Hz, 1H), 7.79-7.85 (m, 1H), 8.08 (s, 1H), 8.12 (s, 2H), 8.65 (d, J=2.37 Hz, 1H), 8.68 (s, 1H), 8.89 (s, 1H), 9.22 (d, J=2.37 Hz, 1H). MS (ESI(+)) m/e 502 $(M+H)^+$.

Example 165

N-{4-[4-amino-7-(3-pyridinyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea

The desired product was prepared by substituting Example 124 for Example 121 in Example 122. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.63 (s, 2H), 7.39-7.47 (m, 3H), 7.53-7.58 (m, 3H), 7.64 (d, J=8.81 Hz, 2H), 7.97 (s, 1H), 8.10 (m, J=8.48, 2.03, 1.70 Hz, 1H), 8.63-8.66 (m, 2H), 8.88 (d, J=1.70 Hz, 1H), 8.98 (d, J=3.05 Hz, 1H), 9.39 (s, 1H). MS (ESI(+)) m/e 524 $(M+H)^+$.

Example 166

N-{4-[4-amino-7-(3-pyridinyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(2-fluoro-5-methylphenyl)urea

The desired product was prepared by substituting Example 124 and 1-fluoro-2-isocyanato-4-methylbenzene for Example 121 and 1-fluoro-2-isocyanato-4-(trfluoromethy)benzene, respectively, in Example 122. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 5.63 (s, 2H), 6.82-6.85 (m, 1H), 7.12 (dd, J=11.53, 8.48 Hz, 1H), 7.42 (d, J=8.48 Hz, 2H), 7.52 (s, 1H), 7.55 (dd, J=8.14, 5.09 Hz, 1H), 7.62 (d, J=8.48 Hz, 2H), 7.96 (s, 1H), 8.00 (dd, J=7.97, 1.86 Hz, 1H), 8.10 (ddd, J=8.14, 2.03, 1.70 Hz, 1H), 8.56 (d, J=2.71 Hz, 1H), 8.62 (dd, J=4.75, 1.36 Hz, 1H), 8.88 (d, J=1.70 Hz, 1H), 9.27 (s, 1H). MS (ESI(+)) m/e 470 $(M+H)^+$.

Examples 167-170 were prepared substituting the appropriate boronic acid (X) for 4-chlorophenylboronic acid in Example 21C.

Example 167

(2E)-3-{4-amino-3-[4-(hydroxymethyl)phenyl]thieno[3,2-c]pyridin-7-yl}-N-methylacrylamide

X= 4-(hydroxymethyl)phenylboronic acid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.73 (d, J=4.4 Hz, 3H), 4.60 (d, J=5.7 Hz, 2H), 5.31 (t, J=5.7 Hz, 1H), 5.81 (s, 2H), 6.58 (d, J=15.9 Hz, 1H), 7.43-7.50 (m, 4H), 7.58 (d, J=15.9 Hz, 1H), 7.64 (s, 1H), 8.12 (s, 1H), 8.15 (q, J=4.4 Hz, 1H), MS (ESI(+)) m/e 340.1 $(M+H)^+$.

Example 168

(2E)-3-[4-amino-3-(3,4-dimethoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-methylacrylamide

X = 3,4-dimethoxyphenylboronic acid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.73 (d, J=4.7 Hz, 3H), 3.79 (s, 3H), 3.83 (s, 3H), 5.88 (s, 2H), 6.57 (d, J=15.9 Hz, 1H), 7.00 (dd, J=8.1, 2.0 Hz, 1H), 7.05 (d, J=2.0 Hz, 1H), 7.11 (d, J=8.5 Hz, 1H), 7.57 (d, J=15.9 Hz, 1H), 7.62 (s, 1H), 8.11 (s, 1H), 8.15 (q, J=4.7 Hz, 1H), MS (ESI(+)) m/e 370.1 $(M+H)^+$.

Example 169

(2E)-3-[4-amino-3-(3-chlorophenyl)thieno[3,2-c]pyridin-7-yl]-N-methylacrylamide

X = 3-chlorophenylboronic acid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.73 (d, J=4.4 Hz, 3H), 5.83 (s, 2H), 6.58 (d, J=15.9 Hz, 1H), 7.44-7.48 (m, 1H), 7.53-7.61 (m, 4H), 7.76 (s, 1H), 8.14 (s, 1H), 8.15 (q, J=4.4 Hz, 1H), MS (ESI(+)) m/e 344.0, 346.2 $(M+H)^+$.

Example 170

(2E)-3-[4-amino-3-(3-chloro-4-fluorophenyl)thieno[3,2-c]pyridin-7-yl]-N-methylacrylamide

X = 3-chloro-4-fluorophenylboronic acid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.73 (d, J=4.7 Hz, 3H), 5.88 (s, 2H), 6.57 (d, J=15.9 Hz, 1H), 7.49 (ddd, J=8.5, 4.9, 2.2 Hz, 1H), 7.56 (t, J=8.8 Hz, 1H), 7.58 (d, J=15.9 Hz, 1H), 7.74 (dd, J=7.1, 2.0 Hz, 1H), 7.75 (s, 1H), 8.14 (s, 1H), 8.14 (q, J=4.7 Hz, 1H), MS (ESI(+)) m/e 362.0, 364.2 $(M+H)^+$.

Example 171

(2E)-3-[4-amino-3-(4-bromophenyl)thieno[3,2-c]pyridin-7-yl]-N-(4-pyridinylmethyl)acrylamide

Example 171A

(2E)-3-[4-amino-3-(4-bromophenyl)thieno[3,2-c]pyridin-7-yl]acrylic acid

The desired compound was prepared by substituting Example 1B for Example 10A in Example 10B, then substituting the product and methylamine for Example 11A and piperazin-2-one, respectively, in Examples 11A-B.

Example 171B

(2E)-3-[4-amino-3-(4-bromophenyl)thieno[3,2-c]pyridin-7-yl]-N-(4-pyridinylmethyl)acrylamide

The desired prodict was prepared as the bis(trifluoroacetate) salt substituting 1-(4-pyridinyl)methanamine and Example 171A for methylamine and Example 13, respectively, in Example 14, then purifying the product by HPLC using the conditions described in Example 82. ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.59 (d, J=5.8 Hz, 2H), 6.57 (s, 2H), 6.81 (d, J=15.9 Hz, 1H), 7.48 (d, J=8.5 Hz, 2H), 7.61 (d, J=5.4 Hz, 2H), 7.68 (d, J=15.9 Hz, 1H), 7.75 (d, J=8.5 Hz, 2H), 7.90 (s, 1H), 8.25 (s, 1H), 8.69 (d, J=6.1 Hz, 2H), 9.02 (t, J=5.8 Hz, 1H). MS (ESI(+)) m/e 465.0, 467.0 $(M+H)^+$.

Examples 172-174 were prepared as the bis(trifluoroacetate) salts by substituting the appropriate amine (X) for 1-(4-pyridinyl)methanamine in Example 171B.

Example 172

3-(4-bromophenyl)-7-[(1E)-3-(4-morpholinyl)-3-oxo-1-propenyl]thieno[3,2-c]pyridin-4-amine

X = morpholine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.59-3.67 (m, 8H), 5.87 (s, 2H), 7.06 (d, J=15.3 Hz, 1H), 7.45 (d, J=8.5 Hz, 2H), 7.67-7.74 (m, 4H), 8.32 (s, 1H).

Example 173

(2E)-3-[4-amino-3-(4-bromophenyl)thieno[3,2-c]pyridin-7-yl]-N-[3-(1H-imidazol-1-yl)propyl]acrylamide

X = 3-(1H-imidazol-1-yl)-1-propanamine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.05 (p, J=7.1, Hz, 2H), 3.23 (q, J=6.2 Hz, 2H), 4.25 (t, J=7.1 Hz, 2H), 6.41 (s, 2H), 6.66 (d, J=15.9 Hz, 1H), 7.47 (d, J=8.5 Hz, 2H), 7.61 (d, J=15.9 Hz, 1H), 7.71 (t, J=1.7 Hz, 1H), 7.75 (d, J=8.5 Hz, 2H), 7.84 (t, J=1.7 Hz, 1H), 7.86 (s, 1H), 8.20 (s, 1H), 8.41 (t, J=5.8 Hz, 1H), 9.14 (s, 1H). MS (ESI(+)) m/e 482.0, 483.8 $(M+H)^+$.

Example 174

(2E)-3-[4-amino-3-(4-bromophenyl)thieno[3,2-c]pyridin-7-yl]-N-[2-(diethylamino)ethyl]acrylamide

X = N,N-diethyl-1,2-ethanediamine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.22 (t, J=7.3 Hz, 6H), 3.17-3.26 (m, 4H), 3.55 (q, J=5.8 Hz, 4H), 6.37 (s, 2H), 6.65 (d, J=15.9 Hz, 1H), 7.46 (d, J=8.5 Hz, 2H), 7.66 (d, J=15.9 Hz, 1H), 7.75 (d, J=8.5 Hz, 2H), 7.84 (s, 1H), 8.22 (s, 1H), 8.58 (t, J=5.6 Hz, 1H), 9.17 (s, 1H, TFA salt-H). MS (ESI(+)) m/e 473.0, 474.9 $(M+H)^+$.

Example 175

N-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1H-indole-3-carboxamide

Example 175A

4-bromo-2-methoxyaniline

A mixture of o-anisidine (27.1g, 219 mmol) and dichloromethane (500 mL) was stirred under an atmosphere of nitrogen and treated with 2,4,4,6-tetrabromo-2,5-cyclohexadienone (90.0g, 219 mmol) in four roughly equal portions over the course of 20 minutes. The temperature of the reaction was maintained between 10 and 15 °C by cooling with a cold water bath during the addition of the 2,4,4,6-tetrabromo-2,5-cyclohexadienone. The mixture was warmed to ambient temperature and stirred for an additional 1.5 hours at which time HPLC [Hypersil HS C18, 5 μm, 100Å, 250 x 4.6 mm; 25-100% acetonitrile/0.1M ammonium acetate over 10 minutes, 1mL/min) o-anisidine t_r=7.63 min, 4-bromo-2-methoxyaniline R_t = 9.77 min] indicated very little o-anisidine remaining. The mixture was washed with 0.67N NaOH (300 mL) and 1N aqueous sodium hydroxide (300 mL). The combined aqueous washes were extracted with dichloromethane (150 mL) and the combined organic solutions were then washed with water (2 x 200 mL) and brine (200 mL), dried ($MgSO_4$), filtered, and concentrated to provide about 48g of the desired product.

Example 175B

tert-butyl 4-bromo-2-methoxyphenylcarbamate

A mixture of Example 175A (36.4g, 180 mmol), and di-tert-butyl dicarbonate (47.2g, 216 mmol) in THF (500 mL) was heated to reflux for 20 hours and cooled to ambient temperature. HPLC (using the conditions from Example 175A, product R_t = 13.55 min and TLC (8:2 heptane/ethyl acetate, R_f of product = 0.53, R_f of 4-bromo-2-methoxyaniline = 0.27) indicated approximately 10% starting material was remaining. Additional di-tert-butyl dicarbonate (3.9g, 18 mmol) was added and heating was continued for another 5 hours. The mixture was cooled and evaporated under reduced pressure. The residue was applied to a 400 gram silica gel column and eluted with 8:2 heptane/ethyl acetate. The fractions showing the desired product were combined and washed with saturated $NaHCO_3$ and then brine. The

organic solution was dried ($MgSO_4$), filtered, and concentrated to provide 61.3g of a mixture of the desired product and di-tert-butyl dicarbonate which was used directly in the next step.

Example 175C

tert-butyl 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate

A mixture of Example 175B (61.3g, 203 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (51.6g, 203 mmol), [1.1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (1:1) (3.2g, 3.9 mmol), and potassium acetate (59.7g, 609 mmol) in DMF (1.0 L) was heated to 80 °C under an atmosphere of nitrogen for 16 hours, cooled to ambient temperature, and concentrated. Dichloromethane (500 mL) was added to the residue and the resulting solid was removed by filtration through a pad of diatomaceous earth (Celite®). The pad was washed with dichloromethane (4 x 50 mL) and the combined filtrates were concentrated, applied to a 550 gram silica gel column, and quickly eluted with heptane/ethyl acetate (85:15) The fractions showing product [R_t with conditions described in Example 175A = 14.33 minutes, R_f of product = 0.33 TLC (85:15 heptane/ethyl acetate), R_f of tert-butyl N-(4-bromo-2-methoxyphenyl)carbamate = 0.48]. This material was treated with heptane (300 mL) and stirred at ambient temperature for 30 minutes. The mixture was cooled to about 5 °C for 3 hours and the resulting precipitate was collected by filtration to provide 24.4g of the desired product. The filtrate was evaporated and the residue was purified by flash chromatography on a 400 gram silica gel column with 9:1 heptane/ethyl acetate to give an additional 8.8g of the desired product.

Example 175D

tert-butyl 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate

A mixture of Example 175C (45.0g, 0.129 mole) in dichloromethane (270 mL) was cooled to <5 °C in an ice bath and treated with a 1:1 solution of TFA/dichloromethane (500 mL) while maintaining the reaction temperature below 5 °C. The reaction was warmed to ambient temperature and stirred for 2 hours. The solvents were removed by evaporation at a pressure of 30 Torr and a bath temperature of <30 °C. The residue was dissolved in dichloromethane (250 mL) and carefully washed with 2.5N sodium hydroxide (300 mL). The organic layer was extracted with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated to provide the desired product (21.7g, 68%). ^1H NMR (DMSO-d_6, 400 MHz) δ 7.05 (d, 1H), 6.98 (d, 1H), 6.59 (d, 1H), 5.13 (s, 2H), 3.75 (s, 3H), 1.25 (s, 12H); reverse phase HPLC (Hypersil HS, 5μm, 100A, 4.6 x 250 mm; 25%-100% acetonitrile/0.05M ammonium acetate over 10 minutes, 1 mL/min) R_t 11.03 min.

Example 175E

N-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1H-indole-3-carboxamide

A mixture of Example 175D (19.75g, 79.3 mmol) in dichloromethane (150 mL) was treated with N,N-diisopropylethylamine (12.3g, 95.2 mmol), cooled to <5 °C with an ice bath, and treated slowly with a solution of 1-methyl-1H-indole-2-carbonyl chloride (87.3 mmol) in dichloromethane (300 mL) while maintaining the reaction temperature below 5 °C. The mixture was warmed to ambient temperature, stirred for 12 hours, extracted twice with water (150 mL, 100 mL), once with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. The material was purified by flash chromatography using 400g of silica gel and 3:1 heptane/ethyl acetate to provide the desired product (30.3g, 94%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.35 (s, 1H), 8.03 (d, 1H), 7.69 (d, 1H), 7.57 (d, 1H), 7.1-7.3 (m, 4H), 7.12 (t, 1H), 4.02 (s, 3H), 3.91 (s, 3H), 1.31 (s, 12H); RP-HPLC (Hypersil HS, 5 μm, 100Å, 4.6 x 250 mm; 25%-100% acetonitrile/0.05M ammonium acetate over 10 min, 1 mL/min) R_t 14.65 min.

Example 176

N-(4-{4-amino-7-[(1E)-3-oxo-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide

Example 176A

3-bromo-7-[(1E)-3,3-diethoxy-1-propenyl]thieno[3,2-c]pyridin-4-amine

A mixture Example 21A (200mg, 0.56 mmol), 2-[(1E)-3,3-diethoxy-1-propenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (175mg, 0.67 mmol), $Pd(PPh_3)_4$ (40mg, 0.03 mmol) and Na_2CO_3 (120mg, 1.13 mmol) in 1,2-dimethoxyethane (10 mL) and water (5 mL) was heated in an 85 °C oil bath for 15 hours. The mixture was cooled to room temperature and concentrated under reduced pressure. The mixture was extracted with dichloromethane and the extract was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel to provide the desired product (150mg, 75%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.02 (s, 1H), 7.88 (s, 1H), 6.74 (d, 1H), 6.09 (dd, 1H), 5.09 (d, 1H), 3.62 (m, 2H), 3.48 (m, 2H), 1.15 (t, 6H); MS m/e 357.1, 359.1 $(M+H)^+$.

Example 176B

N-(4-{4-amino-7-[(1E)-3,3-diethoxy-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide

A mixture of Example 176A (150mg, 0.42 mmol), Example 175E, 255mg, 0.63 mmol), $Pd(PPh_3)_4$ (35mg, 0.03 mmol) and Na_2CO_3 (90mg, 0.84 mmol) in 1,2-

dimethoxyethane (6 mL) and water (3 mL) was heated at reflux for 18 hours. The mixture was cooled to room temperature and concentrated under reduced pressure. The mixture was extracted with dichloromethane then the extract was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography on silica gel to provide the desired product (178mg, 76%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.5 (s, 1H), 8.03 (m, 2H), 7.7 (d, 1H), 7.59 (m, 2H), 7.33 (m, 2H), 7.21 (s, 1H), 7.14 (t, 1H), 7.09 (d, 1H), 6.82 (d, 1H), 6.17 (dd, 1H), 5.14 (d, 1H), 4.03 (s, 3H), 3.91 (s, 3H), 3.65 (m, 2H), 3.53 (m, 2H), 1.17 (t, 6H); MS m/e 557.3 $(M+H)^+$.

Example 176C

N-(4-{4-amino-7-[(1E)-3-oxo-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide

A mixture of Example 176B (90mg, 0.16 mmol) in acetone (9 mL) and water (1 mL) was treated with p-toluenesulfonic acid (5mg, 0.016 mmol) then stirred for 30 minutes. The solvent was evaporated under reduced pressure then the residue was partitioned between dichloromethane and water. The organic layer was concentrated and the residue was purified by flash chromatography on silica gel to provide the desired product (77 mg). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.67 (d, 1H), 9.52 (s, 1H), 8.34 (s, 1H), 8.03 (d, 1H), 7.91 (d, 1H), 7.75 (s, 1H), 7.70 (d, 1H), 7.32 (m, 2H), 7.25 (s, 1H), 7.10 (m, 3H), 6.69 (m, 1H), 4.04 (s, 3H), 3.92 (s, 3H); MS m/e 483.3.

General Procedure for Reductive Aminations

Example 176C (40mg, 0.083 mmol), sodium triacetoxyborohydride (35mg, 0.166 mmol) and the appropriate amine (0.166 mmol) in 1,2-dichloromethane (2 mL) were stirred for 2 to 72 hours at ambient temperature. The mixture was concentrated and the product was purified by normal or reverse phase chromatography.

Example 177

N-(4-{4-amino-7-[(1E)-3-(diethylamino)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide

amine: diethylamine. Reverse phase HPLC (5% to 95% acetonitrile over 25 minutes, 1 mL/min, 254 nm, Hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=19.32 min. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.50 (s, 1H), 8.00 (m, 1H), 7.94 (m, 1H), 7.69 (d, 1H), 7.60 (m, 2H), 7.32 (m, 2H), 7.18 (s, 1H), 7.13 (t, 1H), 7.06 (d, 1H), 6.67 (d, 1H), 6.22 (m, 1H), 5.6 (br s, 2H), 4.02 (s, 3H), 3.89 (s, 3H), 3.32 (d, 2H), 2.52 (q, 4H), 1.01 (t, 6H); MS m/e 540.3 $(M+H)^+$, 538.3 $(M-H)^-$.

Example 178

N-(4-{4-amino-7-[(1E)-3-(ethylamino)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide

amine: ethylamine. Reverse phase HPLC (5% to 95% acetonitrile over 25 minutes, 1 mL/min, 254 nm, Hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=18.46 min. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.50 (s, 1H), 8.01 (m, 1H), 7.94 (s, 1H), 7.70 (d, 1H), 7.61 (s, 1H), 7.58 (d, 1H), 7.35 (s, 1H), 7.33 (m, 1H), 7.20 (s, 1H), 7.15 (t, 1H), 7.07 (d, 1H), 6.65 (d, 1H), 6.28 (m, 1H), 5.60 (br s, 2H), 4.03 (s, 3H), 3.91 (s, 3H), 3.37 (d, 2H), 2.59 (q, 2H), 1.05 (t, 3H); MS m/e 512.4 $(M+H)^+$, 510.5 $(M-H)^-$.

Example 179

N-[4-(4-amino-7-{(1E)-3-[[2-(dimethylamino)ethyl](methyl)amino]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

amine: N,N,N'-trimethyl-1,2-ethanediamine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.50 (s, 1H), 7.99 (d, 1H), 7.96 (s, 1H), 7.72 (d, 1H), 7.6 (m, 2H), 7.35 (m, 2H), 7.33 (m, 2H), 7.21 (s, 1H), 7.14 (t, 1H), 7.07 (d, 1H), 6.24 (m, 1H), 5.64 (br s, 2H), 4.04 (s, 1H), 3.91 (s, 3H), 3.22 (d, 2H), 2.48 (m, 2H), 2.37 (m, 2H), 2.23 (s, 3H), 2.14 (s, 6H); MS m/e 569.4 $(M+H)^+$, 568.5 $(M-H)^-$.

Example 180

N-{4-[4-amino-7-((1E)-3-{[3-(5-methyl-1H-pyrazol-4-yl)propyl]amino}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

amine: 3-(5-methyl-1H-pyrazol-4-yl)-1-propanamine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.50 (s, 1H), 8.00 (t, 1H), 7.93 (s, 1H), 7.71 (d, 1H), 7.61 (s, 1H), 7.58 (d, 1H), 7.33 (m, 3H), 7.2 (s, 1H), 7.15 (t, 1H), 7.08 (d, 1H), 6.65 (d, 1H), 6.28 (m, 1H), 5.59 (br s, 2H), 4.05 (s, 3H), 3.91 (s, 3H), 3.36 (d, 2H), 2.56 (t, 2H), 2.37 (t, 2H), 2.11 (s, 3H), 1.64 (m, 2H); MS m/e 606.3 $(M+H)^+$, 604.3 $(M-H)^-$.

Example 181

N-{4-[4-amino-7-((1E)-3-{[(5-methyl-2-pyrazinyl)methyl]amino}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

amine: (5-methyl-2-pyrazinyl)methylamine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.49 (s, 1H), 8.59 (s, 1H), 8.46 (s, 1H), 8.00 (t, 1H), 7.94 (s, 1H), 7.69 (d, 1H), 7.61 (s, 1H), 7.57 (d, 1H), 7.35 (s, 1H), 7.32 (d, 1H), 7.20 (d, 1H), 7.15 (t, 1H), 7.08 (dd, 1H), 6.67 (d, 1H), 6.28 (m, 1H), 5.61 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.88 (s, 2H), 3.43 (d, 2H), 2.47 (s, 3H); MS m/e 590.3 $(M+H)^+$, 588.4 $(M-H)^-$.

Example 182

N-(4-{4-amino-7-[(1E)-3-(4-phenyl-1-piperazinyl)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide

amine: 1-phenylpiperazine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.50 (s, 1H), 7.99 (m, 2H), 7.69 (d, 1H), 7.62 (s, 1H), 7.58 (d, 1H), 7.33 (m, 2H), 7.20 (m, 3H), 7.15 (t, 1H), 7.08 (d, 1H), 6.93 (d, 2H), 6.72 (m, 2H), 6.27 (m, 1H), 5.65 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.24 (d, 2H), 3.17 (m, 4H), 2.60 (m, 4H); MS m/e 629.4 $(M+H)^+$, 627.4 $(M-H)^-$.

Example 183

N-[4-(4-amino-7-{(1E)-3-[(3-pyridinylmethyl)amino]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

amine: 1-(3-pyridinyl)methanamine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.49 (s, 1H), 8.56 (s, 1H), 8.45 (d, 1H), 8.00 (m, 1H), 7.95 (s, 1H), 7.78 (d, 1H), 7.71 (d, 1H), 7.61 (s, 1H), 7.57 (d, 1H), 7.34 (m, 3H), 7.20 (d, 1H), 7.14 (t, 1H), 7.07 (dd, 1H), 6.66 (d, 1H), 6.30 (m, 1H), 5.61 (br s, 2H), 4.03 (s, 3H), 3.91 (s, 3H), 3.77 (s, 2H), 3.38 (d, 2H); MS m/e 575.3 $(M+H)^+$, 573.5 $(M-H)^-$.

Example 184

N-[4-(4-amino-7-{(1E)-3-[(2-pyridinylmethyl)amino]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

amine: 1-(2-pyridinyl)methanamine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.50 (s, 1H), 8.51 (s, 1H), 8.0 (m, 1H), 7.96 (s, 1H), 7.77 (m, 1H), 7.71 (m,1H), 7.60 (m, 2H), 7.49 (m, 1H), 7.3 (m, 4H), 7.14 (m, 1H), 7.09 (m, 1H), 6.67 (d, 1H), 6.34 (m, 1H), 5.6 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.87 (s, 2H), 3.42 (d, 2H); MS m/e 575.4 $(M+H)^+$, 573.4 $(M-H)^-$.

Example 185

N-{4-[4-amino-7-((1E)-3-{[2-(2-pyridinyl)ethyl]amino}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

amine: 2-(2-pyridinyl)ethanamine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.50 (s, 1H), 8.47 (m, 1H), 8.00 (m, 1H), 7.93 (s, 1H), 7.69 (m, 2H), 7.59 (m, 2H), 7.35 (s, 1H), 7.31 (m, 2H), 7.2 (m, 3H), 7.07 (m, 1H), 6.65 (d, 1H), 6.28 (m, 1H), 5.60 (br s, 2H), 4.03 (s, 3H), 3.91 (s, 3H), 3.45 (m, 2H), 3.42 (d, 2H), 2.85 (m, 2H); MS m/e 587.3 $(M+H)^+$, 588.8 $(M-H)^-$.

Example 186

N-{4-[4-amino-7-((1E)-3-{[2-(1H-indol-3-yl)ethyl]amino}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

amine: 2-(1H-indol-3-yl)ethanamine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.82 (s,

1H), 9.51 (s, 1H), 8.01 (m, 1H), 7.93 (m, 1H), 7.72 (m, 1H), 7.58 (m, 3H), 7.36 (m, 3H), 7.20 (m, 3H), 7.08 (m, 2H), 6.98 (m, 1H), 6.67 (d, 1H), 6.32 (m, 1H), 5.6 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3-3.6 (m, 6H); MS m/e 627.4 $(M+H)^+$, 625.6 $(M-H)^-$.

Example 187

N-(4-{4-amino-7-[(1E)-3-(4-morpholinyl)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide

amine: morpholine. Reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=13 min. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.51 (s, 1H), 8.00 (d, 1H), 7.95 (s, 1H), 7.71 (d, 1H), 7.58-7.62 (m, 2H), 7.05-7.21 (m, 3H), 6.65 (d, 1H), 6.25 (dt, 1H), 5.62 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.61 (t, 4H), 3.19 (d, 2H), 2.44 (m, 4H); MS m/e 554.3 $(M+H)^+$.

Example 188

N-(4-{4-amino-7-[(1E)-3-(4-hydroxy-1-piperidinyl)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide

amine: 4-piperidinol. Purification by reverse phase HPLC using ammonium acetate buffer followed by lyophilization provided the desired product as the diacetate salt. Reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=10.2 min. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.47 (s, 1H), 7.98 (d, 1H), 7.94 (s, 1H), 7.68 (d, 1H), 7.55-7.62 (m, 2H), 7.30-7.32 (m, 2H), 7.04-7.17 (m, 3H), 6.63 (d, 1H), 6.23 (dt, 1H), 5.61 (br s, 2H), 4.01 (s, 3H), 3.89 (s, 3H), 3.12 (d, 2H), 2.73 (m, 2H), 2.06 (t, 2H), 1.85 (s, 6H), 1.70 (m, 2H), 1.38 (q, 2H); MS m/e 568.9 $(M+H)^+$.

Example 189

N-[4-(4-amino-7-{(1E)-3-[ethyl(2-hydroxyethyl)amino]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

amine: 2-(ethylamino)ethanol. Purification by reverse phase HPLC using ammonium acetate buffer followed by lyophilization provided the desired product as the acetate salt. Reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=10.4 min. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.51 (s, 1H), 8.00 (d, 1H), 7.96 (s, 1H), 7.71 (d, 1H), 7.58-7.62 (m, 3H), 7.33-7.35 (m, 2H), 7.07-7.21 (m, 2H), 6.68 (d, 1H), 6.26 (dt, 1H), 5.62 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.50 (t, 2H), 3.32 (d, 2H), 2.56-2.59 (m, 3H), 1.88 (s, 3H), 1.02 (t, 3H); MS m/e 556.4 $(M+H)^+$.

Example 190

N-[4-(4-amino-7-{(1E)-3-[4-(2-hydroxyethyl)-1-piperidinyl]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

amine: 2-(4-piperidinyl)ethanol. Purification by reverse phase HPLC using ammonium acetate buffer followed by lyophilization provided the desired product as the diacetate salt. Reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=10.3 min. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.51 (s, 1H), 8.00 (d, 1H), 7.96 (s, 1H), 7.71 (d, 1H), 7.58-7.62 (m, 2H), 7.33-7.35 (m, 2H), 7.05-7.21 (m, 3H), 6.65 (d, 1H), 6.25 (dt, 1H), 5.62 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.43 (t, 2H), 3.15 (d, 2H), 2.90 (d, 2H), 1.93 (t, 2H), 1.88 (s, 6H), 1.62 (d, 2H), 1.36 (t, 2H), 1.18 (m, 1H); MS m/e 596.8 $(M+H)^+$.

Example 191

N-(4-{7-[(1E)-3-(4-acetyl-1-piperazinyl)-1-propenyl]-4-aminothieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide

amine: 1-acetylpiperazine. Purification by reverse phase HPLC using ammonium acetate buffer followed by lyophilization provided the desired product as the acetate salt. Reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=11.3 min. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.52 (s, 1H), 8.01 (d, 1H), 7.98 (s, 1H), 7.71 (d, 1H), 7.58-7.62 (m, 2H), 7.33-7.35 (m, 2H), 7.05-7.21 (m, 3H), 6.65 (d, 1H), 6.25 (dt, 1H), 5.62 (br s, 2H), 4.04 (s, 3H), 3.92 (s, 3H), 3.46 (t, 4H), 3.22 (d, 2H), 2.42 (dt, 4H), 2.00 (s, 3H), 1.91 (s, 3H); MS m/e 595.4 $(M+H)^+$.

Example 192

N-(4-{4-amino-7-[(1E)-3-(4-methyl-1-piperazinyl)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide

amine: 1-methylpiperazine. Reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=10.6 min. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.51 (s, 1H), 8.01 (d, 1H), 7.97 (s, 1H), 7.71 (d, 1H), 7.58-7.62 (m, 2H), 7.32-7.35 (m, 2H), 7.05-7.21 (m, 3H), 6.68 (d, 1H), 6.23 (dt, 1H), 5.64 (br s, 2H), 4.04 (s, 3H), 3.92 (s, 3H), 3.17 (d, 2H), 2.36-2.46 (m, 4H), 2.17 (s, 3H); MS m/e 567.4 $(M+H)^+$.

Example 193

N-{4-[4-amino-7-((1E)-3-{[2-(1-pyrrolidinyl)ethyl]amino}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

amine: 2-(1-pyrrolidinyl)ethanamine. Purification by reverse phase HPLC using ammonium acetate buffer followed by lyophilization provided the desired product as the

diacetate salt. Reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100Å, C18, 5 μm, 250 x 4.6 column) R_t=11 min. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.51 (s, 1H), 8.00 (d, 1H), 7.95 (s, 1H), 7.71 (d, 1H), 7.62 (s, 1H), 7.59 (d, 1H), 7.33-7.35 (m, 2H), 7.10-7.21 (m, 3H), 6.65 (d, 1H), 6.28 (dt, 1H), 5.64 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.41 (d, 2H), 2.67 (t, 2H), 2.51-2.54 (m, 3H), 2.44 (t, 4H), 1.88 (s, 3H), 1.67 (s, 4H); MS m/e 581.0 $(M+H)^+$.

Example 194

N-{4-[4-amino-7-((1E)-3-{[2-(2-oxo-1-imidazolidinyl)ethyl]amino}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

amine: 1-(2-aminoethyl)-2-imidazolidinone. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.51 (s, 1H), 8.00-8.02 (m, 2H), 7.71 (d, 1H), 7.58-7.62 (m, 2H), 7.05-7.21 (m, 3H), 6.75 (d, 1H), 6.34 (dt, 1H), 5.64 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.37-3.46 (m, 3H), 3.21-3.31 (m, 3H), 3.17 (m, 2H), 2.70 (t, 1H); R_f=0.3 (dichloromethane/methanol/ammonium hydroxide = 9:1:0.003).

Example 195

N-{4-[4-amino-7-((1E)-3-{[2-(1-methyl-2-pyrrolidinyl)ethyl]amino}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

amine: 2-(1-methyl-2-pyrrolidinyl)ethanamine. Purification by reverse phase HPLC using ammonium acetate buffer followed by lyophilization provided the desired product as the diacetate salt. Reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=11 min. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.51 (s, 1H), 8.00 (d, 1H), 7.95 (s, 1H), 7.71 (d, 1H), 7.62 (s, 1H), 7.59 (d, 1H), 7.33-7.35 (m, 2H), 7.07-7.21 (m, 3H), 6.65 (d, 1H), 6.28 (dt, 1H), 5.62 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.40 (d, 2H), 2.90 (m, 1H), 2.55-2.70 (m, 2H), 2.21 (s, 3H), 2.02 (m, 2H), 1.88 (s, 6H), 1.75-1.85 (m, 2H), 1.58-1.68 (m, 2H), 1.35-1.45 (m, 2H); MS m/e 581.0 $(M+H)^+$.

Example 196

N-[4-(4-amino-7-{(1E)-3-[(4-pyridinylmethyl)amino]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

amine: 1-(4-pyridinyl)methanamine. Purification by reverse phase HPLC using ammonium acetate buffer followed by lyophilization provided the desired product as the diacetate salt. Reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=10.6 min. ^{1}H NMR (DMSO-d_6,

400 MHz) δ 9.51 (s, 1H), 8.48-8.52 (m, 4H), 8.00 (d, 1H), 7.95 (s, 1H), 7.58-7.72 (m, 3H), 7.07-7.40 (m, 6H), 6.70 (d, 1H), 6.30 (d, 1H), 5.62 (br s, 2H), 4.27 (d, 2H), 4.04 (s, 3H), 3.92 (s, 3H), 3.39 (d, 2H), 1.90 (s, 3H); MS m/e 575.4 $(M+H)^+$.

Example 197

N-(4-{4-amino-7-[(1E)-3-amino-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide

Example 197A

tert-butyl (2E)-3-(4-amino-3-bromothieno[3,2-c]pyridin-7-yl)-2-propenylcarbamate

A mixture of Example 21A (1.0g, 2.8 mmol), tert-butyl (2E)-3-(tributylstannyl)-2-propenylcarbamate (prepared according to the procedure described in Synthesis, 1991, (12), 1201, 1.5g, 3.36 mmol), and potassium flouride (195mg, 3.36 mmol) in toluene (10 mL) was degassed, treated with $Pd(PPh_3)_4$ (194mg, 0.17 mmol), degassed, and heated to 110°C for 14 hours under a nitrogen atmosphere. The mixture was concentrated and purified by flash chromatography on silica gel with dichloromethane/ethyl acetate (6:4) to provide the desired product (1.3g, 3.36 mmol). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.93 (s, 1H), 7.35 (s, 1H), 6.55 (d, 1H), 6.21 (dt, 1H), 5.81 (br s, 2H), 4.73 (br s, 1H), 3.98 (s, 2H), 1.48 (s, 9H); reverse phase HPLC (5% to 95% acetonitrile over 25 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=15.5 minutes; MS m/e 385.1.

Example 197B

tert-butyl (2E)-3-[4-amino-3-(3-methoxy-4-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}phenyl)thieno[3,2-c]pyridin-7-yl]-2-propenylcarbamate

A mixture of Example 197A (275mg, 0.716 mmol), Example 175E (436mg, 1.074 mmol), Na_2CO_3 (151mg, 1.43 mmol), and $Pd(PPh_3)_4$ (50mg, 0.043 mmol) in 1,2-dimethoxyethane/water (12:6 mL) was heated to 95 °C for 20 hours and partitioned between water (30 mL) and dichloromethane (40 mL). The organic layer was separated and the aqueous layer was further extracted with dichloromethane (2 x 40 mL). The organic layer was filtered to provide some desired product (117 mg). The filtrate was dried ($MgSO_4$), filtered, concentrated, dissolved in dichloromethane (10 mL), and filtered to provide additional desired product (107 mg). The remaining filtrate was purified by flash chromatography on silica gel with dichloromethane/methanol (97:3). Product-containing fractions were filtered to provide another 25 mg of the desired product to provide a total of 249mg (0.430 mmol). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.51 (s, 1H), 8.01 (t, 1H), 7.95 (s, 1H), 7.70-7.72 (d, 1H), 7.58-7.62 (m, 2H), 7.30-7.35 (m, 2H), 7.07-7.21 (m, 3H), 6.59 (d, 1H), 6.21 (dt, 1H), 5.62 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.78 (t, 2H), 1.42 (s, 9H);

reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=19.2 min. MS m/e 584.3 $(M+H)^+$.

Example 197C

N-(4-{4-amino-7-[(1E)-3-amino-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide

A mixture of Example 197B (250mg, 0.43 mmol), 6N HCl (2.5 mL), and acetone (5 mL) was stirred for 3 hours at ambient temperature and heated to 40 °C for 4 hours. The mixture was partitioned between 2N NaOH (10 mL) and dichloromethane (20 mL). The organic layer was separated and the aqueous layer was further extracted with dichloromethane (2 x 20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to provide the desired product (146 mg): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.66 (s, 1H), 8.58-8.60 (d, 1H), 7.95 (m, 1H), 7.70-7.72 (d, 1H), 7.00-7.52 (m, 6H), 6.69 (d, 1H), 6.46 (m, 1H), 4.89 (br s, 2H), 4.14 (s, 3H), 3.98 (s, 3H), 3.60-3.61 (d, 2H); reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=10.1 min. MS m/e 482.4 $(M-H)^-$.

General Procedure for the Preparation of Amides, Sulfonamides, Carbamates and Ureas from Example 197C

A mixture of Example 197C (30mg, 0.062 mmol) in dichloromethane (2 mL) and pyridine (0.1 mL) was treated with the appropriate acid chloride, sulfonyl chloride, or alkylchloroformate (1.2 eq) at ambient temperature. Ureas were prepared in the same manner from Example 197C and the appropriate isocyanate, but pyridine was omitted from the reaction mixture. The mixtures were stirred for 2 hours at ambient temperature and concentrated. The products were purified by normal or reverse phase chromatography.

Example 198

N-(4-{7-[(1E)-3-(acetylamino)-1-propenyl]-4-aminothieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide

starting reagent: acetyl chloride. Reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=11.5 min. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.51 (s, 1H), 8.17 (t, 1H), 8.00 (s, 1H), 7.96 (s, 1H), 7.71 (d, 1H), 7.62 (s, 1H), 7.58 (d, 1H), 7.30-7.35 (m, 2H), 7.21 (s, 1H), 7.07-7.15 (m, 2H), 6.63 (d, 1H), 6.20 (dt, 1H), 5.64 (br s, 2H), 4.04 (s, 3H), 3.93 (br s, 5H), 1.88 (s, 3H); MS m/e 524.2 $(M-H)^-$.

Example 199

N-[4-(4-amino-7-{(1E)-3-[(methylsulfonyl)amino]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

starting reagent: methylsulfonyl chloride. Reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=12.3 min. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.51 (s, 1H), 8.02 (t, 1H), 8.00 (s, 1H), 7.71 (d, 1H), 7.64 (s, 1H), 7.59 (d, 1H), 7.30-7.35 (m, 2H), 7.21 (s, 1H), 7.07-7.15 (m, 2H), 6.75 (d, 1H), 6.20 (dt, 1H), 5.65 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.84 (t, 2H), 2.96 (s, 3H); MS m/e 562.3 $(M+H)^+$.

Example 200

methyl (2E)-3-[4-amino-3-(3-methoxy-4-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}phenyl)thieno[3,2-c]pyridin-7-yl]-2-propenylcarbamate

starting reagent: methyl chloroformate. Reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=12.8 min. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.51 (s, 1H), 8.02 (t, 1H), 7.96 (s, 1H), 7.71 (d, 1H), 7.58-7.62 (m, 2H), 7.50 (t, 1H), 7.30-7.35 (m, 2H), 7.08-7.21 (m, 3H), 6.63 (d, 2H), 6.22 (dt, 1H), 5.65 (br s, 2H), 4.04 (s, 3H), 3.92 (s, 3H), 3.88 (t, 2H), 3.57 (s, 3H); MS m/e 542.3.

Example 201

N-{4-[4-amino-7-((1E)-3-{[(ethylamino)carbonyl]amino}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

starting reagent: isocyanatoethane. Reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=9.9 min. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.51 (s, 1H), 8.0 (d, 1H), 7.95 (s, 1H), 7.71 (d, 1H), 7.62 (s, 1H), 7.58 (d, 1H), 7.30-7.35 (m, 2H), 7.07-7.21 (m, 3H), 6.60 (d, 1H), 6.23 (dt, 1H), 6.11 (t, 1H), 5.89 (t, 1H), 5.62 (br s, 2H), 4.04 (s, 3H), 3.93 (s, 3H), 3.87 (t, 2H), 3.05, (p, 2H), 1.02 (t, 3H); MS m/e 555.4 $(M+H)^+$.

Example 202

N-[4-(4-amino-7-{(1E)-3-[(3-pyridinylcarbonyl)amino]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

starting reagent: nicotinyl chloride. Reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=11.7 min. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.49 (s, 1H), 9.10-9.18 (m, 2H), 8.75, (d, 1H), 8.25 (d, 1H), 8.14 (t, 1H), 8.10 (s, 1H), 7.97 (s, 1H), 7.71 (d, 1H), 7.55-7.62 (m, 2H), 7.58 (d, 1H), 7.29-7.35 (m, 3H), 7.16 (t, 2H), 7.00 (br s, 1H), 6.75 (d, 1H), 6.58 (dt, 1H), 4.21

(t, 2H), 4.04 (s, 3H), 3.93 (s, 3H); MS m/e 587.1 $(M-H)^-$.

Example 203

N-(4-{4-amino-7-[(1E)-3-(isonicotinoylamino)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide

starting reagent: isonicotinyl chloride. Reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=11.8 min. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.50 (s, 1H), 9.16 (t, 1H), 8.75, (m, 2H), 8.00 (d, 2H), 7.83 (m, 2H), 7.71 (d, 1H), 7.58-7.62 (m, 2H), 7.31-7.35 (m, 2H), 7.21 (s, 1H), 7.07-7.16 (m, 3H), 6.73 (d, 1H), 6.33 (dt, 1H), 4.19 (t, 2H), 4.04 (s, 3H), 3.92 (s, 3H); MS m/e 587.7 $(M-H)^-$.

Example 204

N-{4-[4-amino-7-((1E)-3-{[3-(dimethylamino)benzoyl]amino}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

starting reagent: 3-(dimethylamino)benzoyl chloride. Reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=13.8 min. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.47 (s, 1H), 8.74 (t, 1H), 8.00 (m, 2H), 7.68 (d, 1H), 7.55-7.59 (m, 2H), 7.05-7.32 (m, 7H), 6.84-6.86 (m, 1H), 6.67 (d, 1H), 6.30 (dt, 1H), 5.62 (br s, 2H), 4.12 (t, 2H), 4.06 (s, 3H), 3.83 (s, 3H), 2.92 (s, 6H); MS m/e 629.4 $(M-H)^-$.

Example 205

N-[4-(4-amino-7-{(1E)-3-[(anilinocarbonyl)amino]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

starting reagent: isocyanatobenzene. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.49 (s, 1H), 8.56 (s, 1H), 8.00 (d, 1H), 7.96 (d, 1H), 7.69 (d, 1H), 7.61 (s, 1H), 7.57 (d, 1H), 7.41 (d, 1H), 7.33 (s, 1H), 7.32 (m, 1H), 7.22 (m, 3H), 7.14 (t, 1H), 7.07 (m, 1H), 6.89 (t, 1H), 6.67 (d, 1H), 6.43 (t, 1H), 6.28 (m, 1H), 4.02 (s, 3H), 3.96 (m, 2H), 3.90 (s, 3H); MS m/e 603.4 $(M+H)^+$.

Example 206

N-(4-{4-amino-7-[(1E)-3-(benzoylamino)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide

starting reagent: benzoyl chloride. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.43 (s, 1H), 8.79 (t, 1H), 7.94 (m, 2H), 7.76 (m, 2H), 7.64 (s, 1H), 7.55 (s, 1H), 7.40-7.53 (m, 4H), 7.26 (m, 2H), 7.13 (s, 1H), 7.08 (t, 1H), 7.01 (m, 1H), 6.64 (d, 1H), 6.27 (m, 1H), 5.57 (br s, 2H),

4.09 (t, 2H), 3.97 (s, 3H), 3.85 (s, 3H); MS m/e 588.4 $(M+H)^+$.

Example 207

N-[4-(4-amino-7-{(1E)-3-[(phenylsulfonyl)amino]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

starting reagent: benzenesulfonyl chloride. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.49 (s, 1H), 8.0 (t, 1H), 7.85 (m, 3H), 7.69 (d, 1H), 7.60 (m, 5H), 7.34 (s, 1H), 7.32 (d, 1H), 7.19 (d, 1H), 7.14 (t, 1H), 7.06 (d, 1H), 6.60 (d, 1H), 6.02 (m, 1H), 5.65 (br s, 2H), 4.03 (s, 3H), 3.90 (s, 3H), 3.68 (d, 2H); MS m/e 624.3 $(M+H)^+$.

Example 208

benzyl (2E)-3-[4-amino-3-(3-methoxy-4-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}phenyl)thieno[3,2-c]pyridin-7-yl]-2-propenylcarbamate

starting reagent: benzyl chloroformate. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.49 (s, 1H), 8.01 (t, 1H), 7.94 (s, 1H), 7.71 (d, 1H), 7.62 (m, 2H), 7.58 (d, 1H), 7.31-7.39 (m, 5H), 7.21 (s, 1H), 7.15 (t, 1H), 7.08 (d, 1H), 6.63 (d, 1H), 6.23 (m, 1H), 5.64 (br s, 2H), 5.07 (s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.89 (t, 1H); MS m/e 618.4 $(M+H)^+$.

Example 209

N-[4-(4-amino-7-{(1E)-3-[(5-isoxazolylcarbonyl)amino]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

starting reagent: 5-isoxazolecarbonyl chloride. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.49 (s, 1H), 9.32 (t, 1H), 8.76 (d, 1H), 7.98 (m, 2H), 7.71 (s, 1H), 7.69 (d, 1H), 7.58 (d, 1H), 7.34 (s, 1H), 7.32 (m, 1H), 7.20 (d, 1H), 7.14 (d, 1H), 7.12 (d, 1H), 7.08 (dd, 1H), 6.70 (d, 1H), 6.30 (m, 1H), 5.66 (br s, 2H), 4.15 (t, 1H), 4.03 (s, 3H), 3.91 (s, 3H); MS m/e 579.3 $(M+H)^+$.

General Procedure for Suzuki Coupling in Southern Domain

A mixture of Example 21A (0.250g, 0.74 mmol) in 1,2-dimethoxyethane (10 mL) and water (5 mL) was treated with the appropriate boronic acid (0.85 mmol), Na_2CO_3 (0.179g, 1.69 mmol) and $Pd(PPh_3)_4$ (0.081g, 0.07 mmol) at 80 °C for 18 hours. The organic solvent was removed in vacuo and the solid was isolated by filtration and purified by flash column chromatography on silica gel with 2% methanol/dichloromethane to provide the desired product in 40-88 % yield.

Example 210

3-bromo-7-(3-furyl)thieno[3,2-c]pyridin-4-amine

boronic acid: 3-furylboronic acid. ^{1}H NMR (DMSO-d_6, 400MHz) δ 8.09 (d, 2H), 8.08 (t, 1H), 7.89 (s, 1H), 7.82 (t, 1H), 6.99 (dd, 1H), 6.62 (br s, 2H); reverse phase HPLC (Delta Pak C18, 5 μm, 300 Å, 15 cm; 5%-95% acetonitrile/0.1M ammonium acetate over 10 minutes, then isocratic 3 minutes, 1mL/min) R_t =1.50 min.; MS m/e 295, 297.

Example 211

3-bromo-7-(4-pyridinyl)thieno[3,2-c]pyridin-4-amine

boronic acid: 4-pyridinylboronic acid. ^{1}H NMR (DMSO-d_6, 400MHz) δ 8.65 (d, 2H), 8.07 (s, 1H), 7.88 (s, 1H), 7.65 (d, 2H), 6.86 (br s, 2H); reverse phase HPLC (Delta Pak C18, 5 μm, 300 Å, 15 cm; 5%-95% acetonitrile/0.1M ammonium acetate over 10 minutes, 1mL/min) R_t=9.77 minutes; MS m/e 306, 308 $(M+H)^+$.

Example 212

3-bromo-7-(3-pyridinyl)thieno[3,2-c]pyridin-4-amine

boronic acid: 3-pyridinylboronic acid. ^{1}H NMR (DMSO-d_6, 400MHz) δ 8.81 (dd, 1H), 8.60 (dd, 1H), 8.01-8.05 (m, 1H), 7.96 (s, 1H), 7.86 (s, 1H), 7.51-7.55 (m, 1H), 6.75 (br s, 2H); reverse phase HPLC (Delta Pak C18, 5 μm, 300 Å, 15 cm; 5%-95% acetonitrile/0.1M ammonium acetate over 10 minutes, 1mL/min) R_t=9.84 minutes; MS m/e 306, 308 $(M+H)^+$.

Example 213

3-bromo-7-(3-thienyl)thieno[3,2-c]pyridin-4-amine

boronic acid: 3-thienylboronic acid. Reverse phase HPLC (Delta Pak C18, 5 μm, 300 Å, 15 cm; 5%-95% acetonitrile/0.1M ammonium acetate over 10 minutes, then isocratic 3 minutes, 1mL/min) R_t=12.09 min. ^{1}H NMR (DMSO-d_6, 400MHz) δ 8.07 (s, 1H), 7.87 (s, 1H), 7.65-7.78 (m, 1H), 7.69-7.73 (m, 1H), 7.50 (dd, 1H), 6.64 (br s, 2H); MS m/e 311,313 $(M+H)^+$.

Example 214

3-bromo-7-(2-thienyl)thieno[3,2-c]pyridin-4-amine

boronic acid: 2-thienylboronic acid. Reverse phase HPLC (Delta Pak C18, 5 μm, 300 Å, 15 cm; 5%-95% acetonitrile/0.1M ammonium acetate over 10 minutes, then isocratic 3 minutes, 1mL/min) R_t=12.09 min. ^{1}H NMR (DMSO-d_6, 400MHz) δ 8.07 (s, 1H), 7.87 (s, 1H), 7.65-7.78 (m, 1H), 7.69-7.73 (m, 1H), 7.50 (dd, 1H), 6.64 (br s, 2H); MS m/e 311,313 $(M+H)^+$.

Example 215

3-bromo-7-(6-methoxy-3-pyridinyl)thieno[3,2-c]pyridin-4-amine

boronic acid: 6-methoxy-3-pyridinylboronic acid. Reverse phase HPLC (Delta Pak C18, 5 μm, 300 Å, 15 cm; 50%-100% acetonitrile/0.1M ammonium acetate over 10 min, 1mL/min) R_t=6.60 min. ^{1}H NMR (DMSO-d_6, 400MHz) δ 8.37 (dd, 1H), 7.93 (dd, 1H), 7.88 (s, 1H), 7.85 (s, 1H), 6.96 (dd, 1H), 6.66 (br s, 2H), 3.91 (s, 1H); MS m/e 336, 338 $(M+H)^+$.

General Procedure for Suzuki Coupling in Northern Domain

A mixture of the 3-bromothienyl compound (Examples 210-212) (1.0 eq) in 1,2-dimethoxyethane (10 mL) and water (5 mL) was reacted with Example 175E (1.2 eq), Na_2CO_3 (2.4 eq), and $Pd(PPh_3)_4$ (0.06 eq) at 95 °C for 18 hours. The organic solvent was removed in vacuo and the the mixture was extracted with dichloromethane. The extract was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by preparative reverse phase HPLC (Rainin C18, 8 mm, 300 Å, 25 cm; 40% acetonitrile/0.1M ammonium acetate isocratic for 5 minutes, then 40-100% acetonitrile/0.1M ammonium acetate over 30 minutes, 21 mL/min). The acetonitrile was removed in vacuo and the aqueous mixture was lyophilized to provide the desired product.

Example 216

N-{4-[4-amino-7-(4-pyridinyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

bromide: Example 211. ^{1}H NMR (DMSO-d_6, 400MHz) δ 9.52 (s, 1H), 8.69 (d, 2H), 8.12 (s, 1H), 8.03 (t, 1H), 7.68-7.76 (m, 3H), 7.65 (s, 1H), 7.59 (d, 1H), 7.29-7.37 (m, 2H), 7.24 (s, 1H), 7.08-7.18 (m, 2H), 5.75-5.90 (br s, 2H), 4.04 (s, 3H), 3.92 (s, 3H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3mm particle size, 33 x 4.6mm; 30-95% acetonitrile/0.050M ammonium acetate over 3 minutes, then isocratic 95% acetonitrile/0.050M ammonium acetate over 1.5 minutes, 0.8 mL/min): MS m/e 506 $(M+H)^+$, RT = 3.95 min.

Example 217

N-{4-[4-amino-7-(3-furyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

bromide: Example 210. ^{1}H NMR (DMSO-d_6, 400MHz) δ 9.52 (s, 1H), 8.69 (d, 2H), 8.12 (s, 1H), 8.03 (t, 1H), 7.68-7.76 (m, 3H), 7.65 (s, 1H), 7.59 (d, 1H), 7.29-7.37 (m, 2H), 7.24 (s, 1H), 7.08-7.18 (m, 2H), 5.75-5.90 (br s, 2H), 4.04 (s, 3H), 3.92 (s, 3H); reverse phase HPLC (Delta Pak C18, 5 μm, 300 Å, 15 cm; 5%-95% acetonitrile/0.1M ammonium acetate over 10 min, 1mL/min) R_t=8.75 minutes; MS m/e 495 $(M+H)^+$.

Example 218

N-{4-[4-amino-7-(3-pyridinyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

bromide: Example 212. ^{1}H NMR (DMSO-d_6, 400MHz) δ 9.52 (s, 1H), 8.88 (d, 1H), 8.63 (dd, 1H), 8.08-8.13 (m, 1H), 8.02 (t, 1H), 7.99 (s, 1H), 7.71 (d, 1H), 7.54-7.63 (m, 3H), 7.30-7.37 (m, 2H), 7.24 (d, 1H), 7.09-7.18 (m, 2H), 5.67-5.76 (br s, 2H), 4.04 (s, 3H), 3.92 (s, 3H); reverse phase HPLC (Delta Pak C18, 5 μm, 300 Å, 15 cm; 50%-100% acetonitrile/0.1M ammonium acetate over 10 minutes, 1mL/min) R_t=8.50 minutes; MS m/e 506 $(M+H)^+$.

Example 219

3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-4-amine

Example 219A

3-bromothieno[3,2-c]pyridin-4-amine

A mixture of 3-bromo-4-chlorothieno[3,2-c]pyridine (prepared according to the procedure described in *Bull. Soc. Chim. Belges* **1970**, *79*, 407–414, 3g, 12 mmol), concentrated aqueous NH_4OH (100 mL), and p-dioxane (100 mL) was sealed in a stainless steel, high-pressure reactor and stirred for 18 hours at 150 °C. The mixture was concentrated to half its original volume, diluted with water, and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated to provide 2.6g (94%) of the desired product. ^{1}H NMR (DMSO-d_6, 400MHz) δ 7.83 (d, 1H), 7.77 (s, 1H), 7.26 (d, 1H), 6.48 (br s, 2H); MS m/e 229 $(M+H)^+$.

Example 219B

3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-4-amine

A mixture of Example 219A (5.43g, 23.7 mmol), 4-phenoxyphenylboronic acid (6g, 28.03 mmol), Na_2CO_3 (3.7g, 34.9 mmol), $Pd(PPh_3)_4$ (5.4g, 4.7 mmol), DMF (96 mL), and water (24 mL) was stirred for 18 hours at 80 °C under nitrogen, poured into 10% aqueous NaCl (400 mL), and extracted with ethyl acetate (3 x 70 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was dissolved in 300 mL of dichloromethane. Silica gel (90g) was added to the solution and the mixture was concentrated under vacuum. The residual silica gel with the absorbed crude product was transferred to a silica gel column (600g) and chromatographed (eluent 40% ethyl acetate/heptane) to provide 5.61g (75%) of the desired product. ^{1}H NMR (DMSO-d_6, 400MHz) δ 7.85 (d, 1H), 7.49-7.44 (m, 5H), 7.29 (d, 1H), 7.22 (t, 1H), 7.16-7.12 (m, 4H), 5.44 (br s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 156.9, 156.1, 154.5, 148.3, 141.8, 136.1, 130.9, 130.1, 123.9, 123.0, 119.2, 118.4, 118.1, 107.8.

Example 220

N-[4-(4-aminothieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

The desired product was prepared by substituting Example 175E for 4-phenoxyphenylboronic acid in Example 219B. LCMS m/e 429.3 $(M+H)^+$; R_t: 4.05 min.

Example 221

tert-butyl (2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]acrylate

Example 221A

7-iodo-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-4-amine

A solution of Example 219B (5g, 15.7 mmol) in DMF (100 mL) was treated with N-iodosuccinimide (4.23g, 18.8 mmol), stirred at ambient temperature for 2 hours, concentrated to half the original volume, and poured into 5% sodium thiosulfate (400 mL). The mixture was filtered and the filter cake was washed with water and dried. The solids were dissolved in dichloromethane (300 mL), treated with silica gel (80g), and concentrated. The residue was transferred to a silica gel column (600g) and chromatographed with ethyl acetate/heptane (1:6) to provide 5.2 g (75%) of the desired product. ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 7.95 (s, 1H), 7.33–7.29 (m, 4H), 7.12 (s, 1H), 7.10 (t, 1H), 7.02–6.99 (m, 4H), 4.76 (br s, 1H); ^{13}C NMR (CD_2Cl_2, 400 MHz) δ 158.4, 156.8, 154.7, 154.4, 148.6, 138.4, 131.3, 131.2, 130.4, 124.4, 122.9, 120.0, 119,9, 118.8, 72.0.

Example 221B

tert-butyl (2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]acrylate

A mixture of Example 221A (2g, 4.5 mmol), tert-butyl acrylate (1.3 mL, 8.8 mmol), $Pd(OAc)_2$ (100mg, 0.44 mmol), PPh_3 (236mg, 0.89 mmol), Na_2CO_3 (0.95g, 8.9 mmol), and DMF (40 mL) was stirred for 18 hours at 80 °C under a nitrogen atmosphere. The mixture was concentrated to half its original volume and poured into 10% NaCl (300 mL). The product was extracted with ethyl acetate (3 x 70 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was dissolved in dichloromethane (300 mL), treated with silica gel (25g), and concentrated. The preabsorbed silica gel was subsequently transferred to a silica gel (200 g) column and chromatographed with ethyl acetate/heptane (1:6) to provide 1.52 g (76%) of the desired product. ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 8.13 (s, 1H), 7.78 (d, 1H), 7.49-7.43 (m, 4H), 7.32 (s, 1H), 7.22 (t, 1H), 7.15 (d, 4H), 6.46 (d, 1H), 5.18 (br s, 2H), 1.59 (s, 9H); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 166.8, 158.5, 156.8, 155.5, 147.1, 146.9, 139.8, 137.5, 131.3, 130.7, 130.4, 124.4, 123.8, 119.9, 119.7, 118.8, 118.7, 117.2, 80.6, 28.4.

Example 222

butyl (2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]acrylate

The desired product was prepared by substituting butyl acrylate for tert-butyl acrylate in Example 221. LCMS m/e 445.5 $(M+H)^+$; retention time: 5.00 min.

Example 223

ethyl (2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]acrylate

The desired product was prepared by substituting ethyl acrylate for tert-butyl acrylate in Example 221.

Example 224

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-2-propen-1-ol

A solution of Example 223 (0.45g, 10.8 mmol) in THF at -78 °C was treated with 5.4 mL DIBAL-H solution (1.0M in toluene, 5.4 mmol) and methanol (1 mL), warmed to room temperature, and concentrated. The residue was dissolved in methanol (100 mL), treated with silica gel (5g), and concentrated. The preabsorbed silica gel was subsequently transferred to a silica gel column and chromatographed (ethyl acetate/heptane 3:1) to provide 200 mg (49%) of the product.

Example 225

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]acrylic acid

A solution of Example 221B (1.5g, 3.4 mmol) in dichloromethane and trifluoroacetic acid (10 mL) was stirred for 2 hours at ambient temperature, treated with toluene (200 mL), and concentrated to provide 1.7g (100%) of the desired product as the trifluoroacetate salt. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.42 (s, 1H), 7.95 (s, 1H), 7.76 (d, 1H), 7.54 (dd, 2H), 7.46 (dt, 2H), 7.21 (t, 1H), 7.16 (dd, 4H), 6.61 (d, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 167.0, 159.0, 158.6, 157.6, 156.0, 148.8, 137.7, 137.5, 131.0, 130.1, 128.2, 127.6, 124.0, 120.3, 119.4, 119.2, 118.7, 115.7.

Example 226

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]acrylic acid

A solution of Example 225 (1.2g, 2.3 mmol) and p-dioxane (50 mL) was treated with 2.5M HCl. The mixture was stirred for 20 minutes at ambient temperature and concentrated. The process was repeated once more after which the residue was azeotropically dried with toluene (2 x 100 mL) to provide the desired product as the hydrochloride salt.

General Procedure for Amide Formation

Amixture of Example 226 (50mg, 0.12 mmol), N,N-diisopropylethyl amine (90 µL, 5.1 mmol), the amine (0.24 mmol), and DMF (2.5 mL) was treated sequentially with 0.5M HBTU in DMF and 0.5M HOBT in DMF. The reaction was stirred for 18 hours at ambient temperature, diluted with water, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was purified using normal or reverse phase chromatography.

Example 227

tert-butyl 3-[({(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-2-propenoyl}amino)methyl]-1-pyrrolidinecarboxylate

amine: tert-butyl 3-(aminomethyl)-1-pyrrolidinecarboxylate.

Example 228

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-(3-pyrrolidinylmethyl)acrylamide

The desired product was prepared by dissolving Example 227 in dichloromethane (8 mL) and adding TFA (2 mL). The mixture was stirred for 4 hours at room temperature and concentrated to provide the desired product.

Example 229

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-[(3S)-3-pyrrolidinylmethyl]acrylamide

Example 229A

tert-butyl (3R)-3-[({(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-2-propenoyl}amino)methyl]-1-pyrrolidinecarboxylate

amine: tert-butyl (3R)-3-(aminomethyl)-1-pyrrolidinecarboxylate.

Example 229B

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-[(3S)-3-pyrrolidinylmethyl]acrylamide

Example 229A was dissolved in dichloromethane (8 mL), treated with TFA (2 mL), stirred for 4 hours at room temperature, and concentrated to provide the desired product.

Example 230

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-[(3R)-3-

pyrrolidinylmethyl]acrylamide

Example 230A

tert-butyl (3S)-3-[({(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-2-propenoyl}amino)methyl]-1-pyrrolidinecarboxylate

amine: tert-butyl (3S)-3-(aminomethyl)-1-pyrrolidinecarboxylate. ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 8.07 (s, 1H), 7.73 (d, 1H), 7.43–7.37 (m, 4H), 7.25 (s, 1H), 7.16 (t, 1H), 7.09 (d, 4H), 6.47 (d, 1H), 5.94 (br d, 1H), 5.07 (s, 2H), 3.49 (dd, 1H), 3.30–3.26 (m, 1H), 3.04 (m, 1H), 2.45 (m, 1H), 1.99 (m, 1H), 1.70–1.65 (m, 4H), 1.42 (s, 9H).

Example 230B

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-[(3R)-3-pyrrolidinylmethyl]acrylamide

Example 230A was dissolved in dichloromethane (8 mL), treated with TFA (2 mL), stirred for 4 hours at room temperature, and concentrated to provide the desired product. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.31 (m, 1H), 8.12 (s, 1H), 7.67 (s, 1H), 7.64 (d, 1H), 7.57-7.43 (m, 4H), 7.21 (t, 1H), 7.15-7.12 (m, 4H), 6.63 (d, 1H), 5.87 (br s, 2H), 4.15-4.12 (m, 1H), 3.24-3.13 (m, 2H), 2.97-2.87 (m, 1H), 2.82-2.60 (m, 2H), 2.35-2.14 (m, 2H), 1.90-1.80 (m, 1H), 1.80-1.70 (m, 1H); MS m/e 471.

Example 231

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-methylacrylamide

amine: methylamine. ^{1}H NMR (DMSO-d_6, 400MHz) δ 8.16 (q, 1H), 8.13 (s, 1H), 7.66 (s, 1H), 7.58 (d, 1H), 7.51–7.43 (m, 4H), 7.21 (t, 1H), 7.15–7.12 (m, 4H), 6.58 (d, 1H), 5.87 (br s, 2H), 2.73 (d, 3H); MS m/e 402.

Example 232

tert-butyl 3-[({(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-2-propenoyl}amino)methyl]-1-pyrrolidinecarboxylate

amine: tert-butyl 3-(aminomethyl)-1-pyrrolidinecarboxylate.

Example 233

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-(3-pyrrolidinylmethyl)acrylamide

The desired product was prepared by substituting Example 232 for Example 229A in Example 229B.

Example 234

tert-butyl 4-({(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-2-propenoyl}amino)-1-piperidinecarboxylate

amine: tert-butyl 4-amino-1-piperidinecarboxylate.

Example 235

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-4-piperidinylacrylamide

The desired product was prepared by substituting Example 234 for Example 229A in Example 229B. MS m/e 471.3 $(M+H)^+$.

Example 236

tert-butyl 2-[2-({(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-2-propenoyl}amino)ethyl]-1-piperidinecarboxylate

amine: tert-butyl 2-(2-aminoethyl)-1-piperidinecarboxylate.

Example 237

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-[2-(2-piperidinyl)ethyl]acrylamide

The desired product was prepared by substituting Example 236 for Example 229A in Example 229B. MS m/e 499.4 $(M+H)^+$.

Example 238

tert-butyl 3-[({(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-2-propenoyl}amino)methyl]-1-piperidinecarboxylate

amine: tert-butyl 3-(aminomethyl)-1-piperidinecarboxylate.

Example 239

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-(3-piperidinylmethyl)acrylamide

The desired product was prepared by substituting Example 238 for Example 229A in Example 229B. MS m/e 485.3 $(M+H)^+$.

Example 240

tert-butyl 3-({(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-2-propenoyl}amino)-1-pyrrolidinecarboxylate

amine: tert-butyl 3-amino-1-pyrrolidinecarboxylate.

Example 241

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-3-pyrrolidinylacrylamide

The desired product was prepared by substituting Example 241 for Example 229A in Example 229B. MS m/e 457.3 $(M+H)^+$.

Example 242

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-[(3S)-3-pyrrolidinyl]acrylamide

The desired product was prepared by substituting tert-butyl (3S)-3-amino-1-pyrrolidinecarboxylate into the general procedure for amide formation, then substituting the resulting amide for Example 229A in Example 229B. MS m/e 457.2 $(M+H)^+$.

Example 243

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-[(3R)-3-pyrrolidinyl]acrylamide

The desired product was prepared by substituting tert-butyl (3S)-3-amino-1-pyrrolidinecarboxylate into the general procedure for amide formation, then substituting the resulting amide for Example 229A in Example 229B. MS m/e 457.1 $(M+H)^+$.

Example 244

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-[3-(4-morpholinyl)propyl]acrylamide

amine: 3-(4-morpholinyl)-1-propanamine.

Example 245

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-[2-(2-pyridinyl)ethyl]acrylamide

amine: 2-(2-pyridinyl)ethanamine.

Example 246

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-[2-(1-methyl-2-pyrrolidinyl)ethyl]acrylamide

amine: 2-(1-methyl-2-pyrrolidinyl)ethanamine.

Example 247

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-[3-(dimethylamino)propyl]acrylamide

amine: N,N-dimethyl-1,3-propanediamine.

Example 248

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-[3-(1H-imidazol-1-yl)propyl]acrylamide

amine: 3-(1H-imidazol-1-yl)-1-propanamine.

Example 249

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-[3-(1-piperidinyl)propyl]acrylamide

amine: 3-(1-piperidinyl)-1-propanamine.

Example 250

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-(3-pyridinylmethyl)acrylamide

amine: 1-(3-pyridinyl)methanamine.

Example 251

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-[2-(4-morpholinyl)ethyl]acrylamide

amine: 2-(4-morpholinyl)ethanamine.

Example 252

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-[2-(1-pyrrolidinyl)ethyl]acrylamide

amine: 2-(1-pyrrolidinyl)ethanamine.

Example 253

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-[(1-ethyl-2-pyrrolidinyl)methyl]acrylamide

amine: (1-ethyl-2-pyrrolidinyl)methylamine.

Example 254

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-[2-(dimethylamino)ethyl]acrylamide

amine: N,N-dimethyl-1,2-ethanediamine.

Example 255

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-[2-(1-piperidinyl)ethyl]acrylamide

amine: 2-(1-piperidinyl)ethanamine.

Example 256

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-(2-pyridinylmethyl)acrylamide

amine: 1-(2-pyridinyl)methanamine.

Example 257

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-(4-pyridinylmethyl)acrylamide

amine: 1-(4-pyridinyl)methanamine.

Example 258

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-3-piperidinylacrylamide

The desired product was prepared by substituting tert-butyl 3-amino-1-piperidinecarboxylate into the general procedure for amide formation, then substituting the resulting amide for Example 229A in Example 229B.

Example 259

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-[(3R)-3-piperidinyl]acrylamide

The desired product was prepared by substituting tert-butyl (3R)-3-(methylamino)-1-piperidinecarboxylate into the general procedure for amide formation, then substituting the resulting amide for Example 229A in Example 229B.

Example 260

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-N-(4-piperidinylmethyl)acrylamide

The desired product was prepared by substituting tert-butyl 4-(aminomethyl)-1-piperidinecarboxylate into the general procedure for amide formation, then substituting the resulting amide for Example 229A in Example 229B.

General Procedure for Suzuki Coupling

A mixture of Example 10B (50mg, 0.11 mmol), a substituted boronic acid (1.5

equiv.), palladium(II) acetate (2.5mg, 0.011 mmol), PPh_3 (12mg, 0.045 mmol), sodium acetate (35mg, 0.033 mmol), and DMF (2.5 mL) was stirred at 100 °C for 18 hours under a nitrogen atmosphere. The mixture was poured to 50 mL of 10% NaCl in water and the product was extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was dissolved in dichloromethane (100 mL), treated with 2.5g of silica gel, and concentrated. The residue was transferred onto a silica gel column (10 g of silica) and eluted with ethyl acetate/heptane mixtures, typically 1:3, depending on the substrate.

Example 261

7-(2-furyl)-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-4-amine

boronic acid: 2-furylboronic acid. MS m/e 385.3 $(M+H)^+$.

Example 262

7-(3-furyl)-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-4-amine

boronic acid: 3-furylboronic acid. MS m/e 385.3 $(M+H)^+$.

Example 263

7-(1-benzofuran-2-yl)-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-4-amine

boronic acid: 1-benzofuran-2-ylboronic acid. MS m/e 435.2 $(M+H)^+$.

Example 264

5-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-2-furaldehyde

boronic acid: 5-formyl-2-furylboronic acid. MS m/e 413.3 $(M+H)^+$.

Example 265

3-(4-phenoxyphenyl)-7-(1H-pyrrol-3-yl)thieno[3,2-c]pyridin-4-amine

The desired product was prepared by substituting 1-(tert-butoxycarbonyl)-1H-pyrrol-3-ylboronic acid into the general procedure for Suzuki couplings, then substituting the resulting product for Example 229A in Example 229B. MS m/e 384.2 $(M+H)^+$.

Example 266

3-(4-phenoxyphenyl)-7-(1H-pyrrol-2-yl)thieno[3,2-c]pyridin-4-amine

The desired product was prepared by substituting 1-(tert-butoxycarbonyl)-1H-pyrrol-2-ylboronic acid into the general procedure for Suzuki couplings, then substituting the resulting product for Example 229A in Example 229B. MS m/e 384.2 $(M+H)^+$.

Example 267

7-(1H-indol-2-yl)-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-4-amine

The desired product was prepared by substituting 1-(tert-butoxycarbonyl)-1H-indol-2-ylboronic acid into the general procedure for Suzuki couplings, then substituting the resulting product for Example 229A in Example 229B. MS m/e 534.3 $(M+H)^+$ (BOC protected compound).

Example 268

tert-butyl (2E)-3-(4-amino-3-bromothieno[3,2-c]pyridin-7-yl)acrylate

A solution of Example 21A (2.50g, 7.04 mmol), PPh_3 (0.370g, 1.41 mmol), and Na_2CO_3 (1.49g, 14.1 mmol) in DMF (35 mL) was treated with tert-butyl acrylate (2.00 mL, 14.1 mmol) and palladium(II)acetate (0.158g, 0.704 mmol). The reaction was heated to 80 °C under an atmosphere of nitrogen for 16 hours. The reaction was cooled to ambient temperature and partitioned between ethyl acetate (100mL) and brine. The organic phase was washed with brine (2 x 100 mL), dried (Na_2SO_4), filtered, and concentrated. The compound was purified by flash chromatography on silica gel using heptane/ethyl acetate (6:1) to (3:1) to provide the desired product (1.70g, 3.01 mmol). ^{1}HNMR (DMSO-d_6, 400MHz) δ 8.24 (s, 1H), 7.94 (s, 1H), 7.62 (d, 1H), 7.17 (br s, 2H), 6.22 (d, 1H), 1.48 (s, 9H); MS m/e 355/357 $(M+H)^+$.

Example 269

tert-butyl (2E)-3-[4-amino-3-(3-methoxy-4-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}phenyl)thieno[3,2-c]pyridin-7-yl]acrylate

A mixture of Example 268 (1.70g, 4.79 mmol), Example 175E (2.91g, 7.18 mmol), Na_2CO_3 (1.01g, 9.57 mmol), and $Pd(PPh_3)_4$ (0.332g, 0.287 mmol) was heated in a mixture of DME (60 mL) and water (30 mL) at 95 °C for 15 hours under an atmosphere of nitrogen. The reaction was cooled to ambient temperature, treated with additional Example 175E (0.97g, 2.39 mmol) and $Pd(PPh_3)_4$ (0.332g, 0.287 mmol), heated to 95 °C for another 5 hours, and cooled to ambient temperature. The resulting precipitate was collected by filteration and washed with diethyl ether (40mL). The precipiate was dissolved in dichloromethane (200mL), dried (Na_2SO_4), filtered, and concentrated to provide the desired product (1.98g, 3.57 mmol). ^{1}HNMR (DMSO-d_6, 400MHz) δ 9.49 (s, 1H), 8.24 (s, 1H), 8.01 (d, 1H), 7.72 (d, 1H), 7.69 (s, 2H), 7.57 (d, 1H), 7.31 (m, 2H), 7.22 (d, 1H), 7.10 (m, 2H), 6.32 (d, 1H), 6.10 (br s, 2H), 4.03 (s, 3H), 3.91 (s, 3H), 1.51 (s, 9H); MS m/e 555 $(M+H)^+$.

Example 270

(2E)-3-[4-amino-3-(3-methoxy-4-{[(1-methyl-1H-indol-2-

yl)carbonyl]amino}phenyl)thieno[3,2-c]pyridin-7-yl]acrylic acid

The desired product was prepared as the trifluoroacetate salt by substituting Example 269 for Example 221B in Example 225. LCMS m/e 499.2; retention time: 2.08 min.

Example 271

(2E)-3-[4-amino-3-(3-methoxy-4-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}phenyl)thieno[3,2-c]pyridin-7-yl]acrylic acid

The desired product was prepared as the hydrochloride salt by substituting Example 270 for Example 225 in Example 226.

Example 272

N-{4-[4-amino-7-((1E)-3-oxo-3-{[2-(1-piperidinyl)ethyl]amino}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

A mixture of Exmaple 271 (30.6mg, 0.044 mmol), N,N-diisopropylethylamine (35 µL, 0.20 mmol), 2-piperidin-1-ylethylamine (14.3 µL, 0.10 mmol), and DMF (1 mL) was treated sequentially with 0.5M (0.09 mL) of HBTU in DMF and 0.5M (0.09 mL) of HOBT in DMF. The reaction was stirred for 24 hours at ambient temperature and partitioned between 1N NaOH and ethyl acetate. The combined extracts were dried (Na_2SO_4), filtered, and concentrated to provide the desired product (20.4mg, 0.034 mmol). LCMS m/e 609.2; retention time: 2.93 min.

Example 273

N-(4-{4-amino-7-[(1Z)-3-oxo-3-(4-piperidinylamino)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide

Amixture of Example 272 (50mg, 0.12 mmol), N,N-diisopropylethylamine (90 µL, 5.1 mmol), 4-piperidinamine (0.24 mmol), and DMF (2.5 mL) was treated sequentially with 0.5M HBTU in DMF and 0.5M HOBt in DMF. The reaction was stirred for 18 hours at ambient temperature, diluted with water, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was purified using normal or reverse phase chromatography. LCMS m/e 581.3; R_t = 2.67 min.

Example 274

N-[4-(4-amino-7-{(1Z)-3-oxo-3-[(3-piperidinylmethyl)amino]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

A mixture of Example 270 (11mg, 0.020 mmol), tert-butyl 3-(aminomethyl)-1-piperidinecarboxylate (5mg, 0.024 mmol), and Na_2CO_3 (0.060 mmol, 6 mg) in dichloromethane (1 mL) and water (0.5 mL) was treated with a solution of

tetramethylfluoroformadinium hexafluorophosphate (TFFH, 8mg, 0.030 mmol) in dichloromethane (0.5 mL), stirred for 3 days at ambient temparature, treated with additional amine (12mg, 0.056 mmol), stirred another day, treated with additional TFFH (30mg, 0.11 mmol), and partitioned between dichloromethane and saturated $NaHCO_3$. The combine organic phases were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by reversed phase HPLC. The acetonitrile was removed under vacuum and the residue was lyophilized to provide the BOC-protected amine which was dissolved in dichloromethane (1 mL), triethylsilane (0.2 mL), and trifluoroacetic acid (0.5 mL). The mixture was stirred at room temperature for 1 hour and concentrated. The residue was purified by reverse phase HPLC. The acetonitrile was removed under vacuum and the desired product was isolated by lyophylization (1.9 mg). LCMS m/e 595.2; R_t = 2.67 min.

Example 275

(2E)-3-[4-amino-3-(4-bromophenyl)thieno[3,2-c]pyridin-7-yl]-N-3-pyridinylacrylamide

The desired product was prepared as the tris(trifluoroacetate) salt by substituting 3-pyridinamine for 1-(4-pyridinyl)methanamine in Example 171B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.75 (s, 2H), 6.93 (d, J=15.9 Hz, 1H), 7.50 (d, J=8.1 Hz, 2H), 7.56 (dd, J=8.5, 4.7 Hz, 1H), 7.76 (d, J=8.1 Hz, 2H), 7.84 (d, J=15.9 Hz, 1H), 7.97 (s, 1H), 8.25-8.28 (m, 1H), 8.33 (s, 1H), 8.39 (dd, J=5.1, 1.0 Hz, 1H), 9.00 (d, J=2.0 Hz, 1H), 10.76 (s, 1H). MS (ESI(+)) m/e 450.9, 452.8 $(M+H)^+$.

Example 276

3-(1H-indol-5-yl)thieno[3,2-c]pyridin-4-amine

The desired product was prepared by substituting 1H-indol-5-ylboronic acid and Example 1B for 4-chlorophenylboronic acid and Example 21B, respectively, in Example 21C.^{1}H NMR (300 MHz, DMSO-d_6) δ 5.37 (s, 2H), 6.50 (ddd, J=3.0, 2.0, 1.0 Hz, 1H), 7.13 (dd, J=8.5, 1.7 Hz, 1H), 7.24 (d, J=5.4 Hz, 1H), 7.38 (s, 1H), 7.45-7.46 (m, 1H), 7.52 (dt, J=8.5, 1.0 Hz, 1H), 7.60-7.61 (m, 1H), 7.81 (d, J=6.1 Hz, 1H), 11.31 (s, 1H), MS (ESI(+)) m/e 265.9 $(M+H)^+$.

Example 277

N-{4-[4-amino-7-(hydroxymethyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(3-methylphenyl)urea

Example 277A

3-(4-bromo-2-thienyl)-2-butenoic acid

A solution of ethyl (diethoxyphosphino)acetate (34 mL, 171 mmol) in THF (35 mL) was added dropwise via addition funnel, over 20 minutes, to a 0 °C suspension of NaH (6.9g,

60% oil dispersion , 172 mmol) in THF (200 mL). The resulting mixture was stirred at 0 °C for 30 minutes, then treated with a solution of 1-(4-bromo-2-thienyl)ethanone (23.6g, 115 mmol) in THF (75 mL). The reaction was warmed to room temperature, stirred for 4 hours, quenched with water, neutralized with 2N HCl, and extracted three times with ethyl acetate. The combined extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The concentrate was dissolved in ethanol (350 mL) and THF (190 mL), treated with 2N LiOH (115 mL), stirred overnight at room temperature, and concentrated. The remaining aqueous solution was washed with diethyl ether, acidified with 2N HCl, and filtered. The filter cake was washed with water and dried to provide 22.38 g (79% yield) of the desired product as a mixture of E and Z isomers. MS (ESI(+)) m/e 244.7, 246.7 $(M+H)^+$.

Example 277B

3-bromo-7-methylthieno[3,2-c]pyridin-4(5H)-one

The desired product was prepared by substituting Example 277A for (2E)-3-(4-bromo-2-thienyl)acrylic acid in Example 1A. MS (ESI(+)) m/e 244, 246 $(M+H)^+$.

Example 277C

3-bromo-4-chloro-7-methylthieno[3,2-c]pyridine

A solution of Example 277B (10,25g, 42.1 mmol) in $POCl_3$ (50 mL) was stirred at reflux for 2 hours, cooled to room temperature, diluted with ice water, and stirred vigorously resulting in a precipitate which was collected by filtration. The filter cake was further purified by silica gel chromatography on silica gel with dichloromethane to provide 7.14g (64% yield) of the desired product. MS (ESI(+)) m/e 261.9, 263.9 $(M+H)^+$.

Example 277D

(3-bromo-4-chlorothieno[3,2-c]pyridin-7-yl)methyl acetate

A solution of Example 277C (1g, 3.81 mmol) in CCl_4 (30 mL) was treated with NBS (0.755g, 4.24 mmol) and benzoyl peroxide (0.093g, 0.38 mmol), heated to reflux for 24 hours, cooled to room temperature, and filtered. The filtrate was concentrated to provide 3-bromo-7-(bromomethyl)-4-chlorothieno[3,2-c]pyridine, which was used directly. MS (ESI(+)) m/e 339.5, 341.6, 343.4 $(M+H)^+$. The crude product was dissolved in DMF (7.5 mL), treated with sodium acetate (1.6g, 19.5 mmol), heated to 100 °C overnight, and partitioned between water and ethyl acetate. The organic extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel chromatography with 10% ethyl acetate/hexanes to provide0.65 g (53% yield) of the desired product. MS (ESI(+)) m/e 319.7, 321.7, 323.7 $(M+H)^+$.

Example 277E

(4-amino-3-bromothieno[3,2-c]pyridin-7-yl)methanol

A mixture of Example 277D (3.1g, 9.7 mmol), concentrated NH_4OH (62 mL), and dioxane (62 mL) was heated to 150 °C in a sealed tube for 36 hours, filtered, and concentrated to provide a soid which was triturated with water (20 mL), collected and dried to give 2.1g (84% yield) of the desired product. MS (ESI(+)) m/e 258.9, 260.8 $(M+H)^+$.

Example 277F

N-{4-[4-amino-7-(hydroxymethyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(3-methylphenyl)urea

The desired product was prepared by substituting Example 277E and Example 66D for Example 1B and 4-phenoxyphenylboronic acid respectively, in Example 10A. ^1H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 4.61 (d, J=5.4 Hz, 2H), 5.15 (t, J=5.3 Hz, 1H), 5.37 (s, 2H), 6.80 (d, J=7.5 Hz, 1H), 7.17 (t, J=7.6 Hz, 1H), 7.25 (d, J=8.8 Hz, 1H), 7.32 (s, 1H), 7.36 (d, J=8.5 Hz, 2H), 7.44 (s, 1H), 7.60 (d, J=8.5 Hz, 2H), 7.75 (s, 1H), 8.67 (s, 1H), 8.87 (s, 1H). MS (ESI(+)) m/e 405.1 $(M+H)^+$.

Example 278

N-{4-[4-amino-7-(4-morpholinylmethyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(3-methylphenyl)urea

Example 278A

4-amino-3-bromothieno[3,2-c]pyridine-7-carbaldehyde

A solution of Example 277E (1g, 3.86 mmol) in THF (100 mL) was treated with MnO_2 (2.66g, 42.1 mmol), stirred overnight at room temperature, and filtered through diatomaceous earth (Celite®). The pad was washed with THF and dichloromethane and the combined filtrates were concentrated to provide 0.88g (89% yield) of the desired product. MS (ESI(+)) m/e 256.8, 258.8 $(M+H)^+$.

Example 278B

3-bromo-7-(4-morpholinylmethyl)thieno[3,2-c]pyridin-4-amine

A solution of Example 278A (0.048g, 0.187 mmol) in THF (15 mL) and dichloromethane (15 mL) was treated with acetic acid (0.012 mL, 0.21 mmol), morpholine (0.02 mL, 0.23 mmol), and sodium triacetoxyborohydride (0.063g, 0.3 mmol), stirred at room temperature overnight, treated with additional morpholine (0.08 mL), acetic acid (0.05 mL) and sodium triacetoxyborohydride (0.23g), and stirred an additional 8 hours. The reaction was quenched with 1N NaOH and extracted three times with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated and the residue was purified

by preparative HPLC on a Waters Symmetry C8 column (25mm x 100mm, 7μm particle size) using a gradient of 10% to 90% acetonitrile: 0.1% aqueous TFA over 30 minutes to provide 0.045 g (55% yield) of the desired product. MS (ESI(+)) m/e 327.9, 329.8 $(M+H)^+$.

Example 278C

N-{4-[4-amino-7-(4-morpholinylmethyl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(3-methylphenyl)urea

The desired product was prepared by substituting Example 278B and Example 66D for Example 1B and 4-phenoxyphenylboronic acid respectively, in Example 10A. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 2.37-2.40 (m, 4H), 3.56-3.63 (m, 6H), 5.36 (s, 2H), 6.80 (d, J=7.8 Hz, 1H), 7.14-7.19 (m, 1H), 7.24-7.27 (m, 1H), 7.31 (s, 1H), 7.36 (d, J=8.5 Hz, 2H), 7.40 (s, 1H), 7.58 (d, J=8.8 Hz, 2H), 7.70 (s, 1H), 8.66 (s, 1H), 8.84 (s, 1H); MS (ESI(+)) m/e 474.1 $(M+H)^+$.

Example 279

N-(4-{4-amino-7-[(3-oxo-1-piperazinyl)methyl]thieno[3,2-c]pyridin-3-yl}phenyl)-N'-(3-methylphenyl)urea

The desired product was prepared substituting piperazin-2-one for morpholine in Examples 278B-C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 2.58 (t, J=5.1 Hz, 2H), 2.95 (s, 2H), 3.13-3.20 (m, 2H), 3.67 (s, 2H), 5.40 (s, 2H), 6.80 (d, J=7.5 Hz, 1H), 7.17 (t, J=7.8 Hz, 1H), 7.25 (d, J=8.1 Hz, 1H), 7.31 (s, 1H), 7.37 (d, J=8.5 Hz, 2H), 7.40 (s, 1H), 7.59 (d, J=8.5 Hz, 2H), 7.72 (s, 1H), 7.77 (s, 1H), 8.68 (s, 1H), 8.86 (s, 1H); MS (ESI(+)) m/e 487.1 $(M+H)^+$.

Example 280

N-[4-(4-amino-7-{[(2-methoxyethyl)amino]methyl}thieno[3,2-c]pyridin-3-yl)phenyl]-N'-(3-methylphenyl)urea

The desired product was prepared substituting 2-methoxyethylamine for morpholine in Examples 278B-C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 2.65 (t, J=5.6 Hz, 2H), 3.25 (s, 3H), 3.42 (t, J=5.6 Hz, 2H), 3.86 (s, 2H), 5.31 (s, 2H), 6.80 (d, J=7.6 Hz, 1H), 7.17 (t, J=7.6 Hz, 1H), 7.25 (d, J=8.5 Hz, 1H), 7.31 (s, 1H), 7.36 (d, J=8.5 Hz, 2H), 7.40 (s, 1H), 7.59 (d, J=8.8 Hz, 2H), 7.73 (s, 1H), 8.65 (s, 1H), 8.84 (s, 1H); MS (ESI(+)) m/e 462.1 $(M+H)^+$.

Example 281

N-{4-[4-amino-7-(6-methoxy-3-pyridinyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

A mixture of Example 215 (1.0 eq) in 1,2-dimethoxyethane (10 mL) and water (5 mL) was reacted with N-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1H-indole-2-carboxamide (1.2 eq), Na_2CO_3 (2.4 eq), and $Pd(PPh_3)_4$ (0.06 eq) at 95 °C for 18 hours. The organic solvent was removed in vacuo and the the mixture was extracted with dichloromethane. The extract was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by preparative reverse phase HPLC (Rainin C18, 8 mm, 300 Å, 25 cm; 40% acetonitrile/0.1M ammonium acetate isocratic for 5 minutes, then 40-100% acetonitrile/0.1M ammonium acetate over 30 minutes, 21 mL/min). The acetonitrile was removed in vacuo and the aqueous mixture was lyophilized to provide the desired product. ^{1}H NMR (DMSO-d_6, 400MHz) δ 9.52 (s, 1H), 8.45 (s, 1H), 8.02 (t, 1H), 7.91 (s, 1H), 7.71 (d, 1H), 7.55-7.63 (m, 2H), 7.28-7.38 (m, 2H), 7.23 (s, 1H), 7.08-7.18 (m, 2H), 7.03 (d, 1H), 5.57-5.69 (br s, 2H), 4.04 (s, 3H), 3.93 (s, 3H), 3.92 (s, 3H); reverse phase HPLC (Delta Pak C18, 5 μm, 300 Å, 15 cm; 50%-100% acetonitrile/0.1M ammonium acetate over 10 min, 1mL/min) R_t=9.30 min.; MS m/e 536 $(M+H)^+$.

Example 282

N-{4-[4-amino-7-(3-thienyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

A mixture of Example 213 (1.0 eq) in 1,2-dimethoxyethane (10 mL) and water (5 mL) was reacted with Example 175E (1.2 eq), Na_2CO_3 (2.4 eq), and $Pd(PPh_3)_4$ (0.06 eq) at 95 °C for 18 hours. The organic solvent was removed in vacuo and the the mixture was extracted with dichloromethane. The extract was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by preparative reverse phase HPLC (Rainin C18, 8 mm, 300 Å, 25 cm; 40% acetonitrile/0.1M ammonium acetate isocratic for 5 minutes, then 40-100% acetonitrile/0.1M ammonium acetate over 30 minutes, 21 mL/min). The acetonitrile was removed in vacuo and the aqueous mixture was lyophilized to provide the desired product. ^{1}H NMR (DMSO-d_6, 400MHz) δ 9.52 (s, 1H), 8.11 (s, 1H), 8.01 (t, 1H), 7.80-7.85 (m, 1H), 7.72-7.77 (m, 1H), 7.70 (d, 1H), 7.62 (s, 1H), 7.55-7.61 (m, 2H), 7.29-7.36 (m, 2H), 7.22 (d, 1H), 7.07-7.17 (m, 2H), 5.56-5.67 (br s, 2H), 4.04 (s, 3H), 3.92 (s, 3H); RP-HPLC (Delta Pak C18, 5 μm, 300 Å, 15 cm; 50%-100%, acetonitrile/0.1M ammonium acetate over 10 min, 1mL/min) R_t =1.82 min.; MS m/e 511 $(M+H)^+$.

Example 283

N-{4-[4-amino-7-(2-thienyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

A mixture of Example 214 (1.0 eq) in 1,2-dimethoxyethane (10 mL) and water (5 mL)

was reacted with Example 175E (1.2 eq), Na_2CO_3 (2.4 eq), and $Pd(PPh_3)_4$ (0.06 eq) at 95 °C for 18 hours. The organic solvent was removed in vacuo and the the mixture was extracted with dichloromethane. The extract was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by preparative reverse phase HPLC (Rainin C18, 8 mm, 300 Å, 25 cm; 40% acetonitrile/0.1M ammonium acetate isocratic for 5 minutes, then 40-100% acetonitrile/0.1M ammonium acetate over 30 minutes, 21 mL/min). The acetonitrile was removed in vacuo and the aqueous mixture was lyophilized to provide the desired product. ^1H NMR (DMSO-d_6, 400MHz) δ 9.51 (s, 1H), 8.12 (s, 1H), 8.02 (t, 1H), 7.70 (d, 1H), 7.65 (s, 1H), 7.61 (dd, 1H), 7.59 (d, 1H), 7.49 (dd, 1H), 7.30-7.37 (m, 2H), 7.21-7.26 (m, 2H), 7.15 (t, 1H), 7.11 (dd, 1H), 5.68-5.77 (br s, 2H), 4.04 (s, 3H), 3.92 (s, 3H); reverse phase HPLC (Delta Pak C18, 5 μm, 300 Å, 15 cm; 50%-100% acetonitrile/0.1M ammonium acetate over 10 min, 1mL/min) R_t=9.61 min.; MS m/e 511 $(M+H)^+$.

Example 284

N-{4-[4-amino-7-(1H-indol-5-yl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea

Example 284A

3-(4-aminophenyl)-7-(1H-indol-5-yl)thieno[3,2-c]pyridin-4-amine

The desired product was prepared by substituting Example 77B and 1H-indol-5-ylboronic acid for Example 77A and 4-pyridylboronic acid, respectively, in Example 121A. MS (ESI(+)) m/e 357 $(M+H)^+$.

Example 284B

N-{4-[4-amino-7-(1H-indol-5-yl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea

The desired product was prepared by substituting Example 284A for Example 121B in Example 122. ^1H NMR (300 MHz, DMSO-d_6) δ 5.43 (s, 2H), 6.51 (s, 1H), 7.37-7.39 (m, 1H), 7.42-7.44 (m, 3H), 7.47-7.50 (m, 2H), 7.53-7.55 (m, 2H), 7.64 (d, *J*=8.48 Hz, 2H), 7.80 (d, *J*=1.70 Hz, 1H), 7.89 (s, 1H), 8.65 (dd, *J*=7.29, 2.20 Hz, 1H), 8.98 (d, *J*=3.05 Hz, 1H), 9.39 (s, 1H), 11.22 (s, 1H); MS (ESI(+)) m/e 562 $(M+H)^+$.

Example 285

N-{4-[4-amino-7-(1H-indol-5-yl)thieno[3,2-c]pyridin-3-yl]phenyl}-N'-(3-methylphenyl)urea

The desired product was prepared by substituting Example 284A and 1-isocyanato-3-methylbenzene for Example 121B and 1-fluoro-2-isocyanato-4-(trifluoromethyl)benzene, respectively in Example 122. ^1H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 5.42 (s, 2H),

6.51 (s, 1H), 6.81 (d, J=7.12 Hz, 1H), 7.17 (t, J=7.63 Hz, 1H), 7.26-7.28 (m, 1H), 7.32 (s, 1H), 7.36 (dd, J=8.31, 1.87 Hz, 1H), 7.41-7.43 (m, 3H), 7.45 (s, 1H), 7.53 (d, J=8.14 Hz, 1H), 7.62 (d, J=8.82 Hz, 2H), 7.79 (d, J=1.36 Hz, 1H), 7.88 (s, 1H), 8.66 (s, 1H), 8.86 (s, 1H), 11.21 (s, 1H); MS (ESI(+)) m/e 490 $(M+H)^+$.

Examples 286-288 were prepared by substituting the appropriate boronic acid (X) for 4-chloro-phenylboronic acid in Example 21C.

Example 286

(2E)-3-[4-amino-3-(1H-indol-6-yl)thieno[3,2-c]pyridin-7-yl]-N-methylacrylamide

X= 1H-indol-6-ylboronic acid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.74 (d, J=4.4 Hz, 3H), 5.84 (s, 2H), 6.53-6.55 (m, 1H), 6.59 (d, J=15.9 Hz, 1H), 7.07 (dd, J=8.1, 1.4 Hz, 1H), 7.45-7.48 (m, 2H), 7.59 (d, J=15.9 Hz, 1H), 7.62 (s, 1H), 7.69 (d, J=8.1 Hz, 1H), 8.11 (s, 1H), 8.16 (q, J=4.4 Hz, 1H), 11.32 (s, 1H); MS (ESI(+)) m/e 349.0 $(M+H)^+$.

Example 287

(2E)-3-[4-amino-3-(1-methyl-1H-indol-6-yl)thieno[3,2-c]pyridin-7-yl]-N-methylacrylamide

X= 1-methyl-1H-indol-6-ylboronic acid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.74 (d, J=4.4 Hz, 3H), 3.87 (s, 3H), 5.81 (s, 2H), 6.51 (dd, J=3.4, 0.7 Hz, 1H), 6.58 (d, J=15.9 Hz, 1H), 7.22 (dd, J=8.1, 1.7 Hz, 1H), 7.46 (d, J=3.4 Hz, 1H), 7.56-7.64 (m, 4H), 8.10 (s, 1H), 8.15 (q, J=4.4 Hz, 1H); MS (ESI(+)) m/e 363.0 $(M+H)^+$.

Example 288

(2E)-3-[4-amino-3-(2-methyl-1H-indol-5-yl)thieno[3,2-c]pyridin-7-yl]-N-methylacrylamide

X= 2-methyl-1H-indol-5-ylboronic acid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.42 (s, 3H), 2.73 (d, J=4.4 Hz, 3H), 5.82 (s, 2H), 6.20 (s, 1H), 6.58 (d, J=15.9 Hz, 1H), 7.05 (dd, J=8.5, 1.7 Hz, 1H), 7.41 (d, J=8.5 Hz, 1H), 7.47 (d, J=1.4 Hz, 1H), 7.56 (s, 1H), 7.58 (d, J=15.9 Hz, 1H), 8.09 (s, 1H), 8.15 (q, J=4.4 Hz, 1H), 11.17 (s, 1H); MS (ESI(+)) m/e 463.0 $(M+H)^+$.

Example 289

4-{[4-amino-3-(1H-indol-5-yl)thieno[3,2-c]pyridin-7-yl]methyl}-2-piperazinone

The desired product was prepared by substituting piperazin-2-one for morpholine in Example 278B, then substituting the product for Example 21B in Example 29. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.63 (t, J=5.3 Hz, 2H), 2.98 (s, 2H), 3.17-3.22 (m, 2H), 3.71 (s, 2H), 5.82 (s, 2H), 6.51 (m, 1H), 7.15 (dd, J=8.5, 1.7 Hz, 1H), 7.46-7.47 (m, 1H), 7.51 (s, 1H), 7.53 (d,

J=8.5 Hz, 1H), 7.63 (s, 1H), 7.74-7.79 (m, 2H), 11.33 (s, 1H); MS (ESI(+)) m/e 378.1 $(M+H)^+$.

Example 290

N-(4-{4-amino-7-[(3-oxo-1-piperazinyl)methyl]thieno[3,2-c]pyridin-3-yl}phenyl)-N'-[3-(trifluoromethyl)phenyl]urea

The desired product was prepared substituting piperazin-2-one for morpholine in Example 278B, then substituting the product and N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-N'-[3-(trifluoromethyl)phenyl]urea for Example 1B and 4-phenoxyphenylboronic acid, respectively, in Example 10A. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.57-2.60 (m, 2H), 2.95 (s, 2H), 3.15-3.19 (m, 2H), 3.67 (s, 2H), 5.40 (s, 2H), 7.32 (d, J=7.8 Hz, 1H), 7.39 (d, J=8.5 Hz, 2H), 7.41 (s, 1H), 7.53 (t, J=8.0 Hz, 1H), 7.58-7.63 (m, 3H), 7.72 (s, 1H), 7.77 (s, 1H), 8.03 (s, 1H), 9.00 (s, 1H), 9.13 (s, 1H); MS (ESI(+)) m/e 541.1 $(M+H)^+$.

Example 291

(2E)-3-[4-amino-3-(1H-indol-5-yl)thieno[3,2-c]pyridin-7-yl]-N-(4-pyridinylmethyl)acrylamide

Example 291A

(2E)-3-(4-amino-3-bromothieno[3,2-c]pyridin-7-yl)acrylic acid

The desired product was prepared substituting Example 1B for Example 10A in Example 10B, then substituting the product for Example 10B in Examples 11A-B. MS (ESI(+)) m/e 298.8, 300.8 $(M+H)^+$.

Example 291B

(2E)-3-[4-amino-3-(1H-indol-5-yl)thieno[3,2-c]pyridin-7-yl]-N-(4-pyridinylmethyl)acrylamide

The desired product was prepared substituting Example 291A for Example 78 in Example 90, then substituting the product for Example 21B in Example 29. ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.46 (d, J=6.0 Hz, 2H), 5.87 (s, 2H), 6.51-6.53 (m, 1H), 6.70 (d, J=15.9 Hz, 1H), 7.16 (dd, J=8.1, 1.7 Hz, 1H), 7.32 (d, J=5.8 Hz, 2H), 7.47-7.49 (m, 1H), 7.55 (d, J=8.5 Hz, 1H), 7.60 (s, 1H), 7.65 (m, 2H), 8.13 (s, 1H), 8.52 (d, J=5.8 Hz, 2H), 8.83 (t, J=6.0 Hz, 1H), 11.35 (s, 1H).

Example 292

(2E)-3-[4-amino-3-(1H-indol-5-yl)thieno[3,2-c]pyridin-7-yl]-N-[3-(1H-imidazol-1-

yl)propyl]acrylamide

The desired product was prepared substituting Example 291A for Example 78 in Example 96, then substituting the product for Example 21B in Example 29. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.88-1.97 (m, 2H), 3.15-3.21 (m, 2H), 4.03 (t, *J*=7.0 Hz, 2H), 5.83 (s, 2H), 6.52 (m, 1H), 6.60 (d, *J*=15.9 Hz, 1H), 6.90 (t, *J*=1.0 Hz, 1H), 7.16 (dd, *J*=8.5, 1.7 Hz, 1H), 7.22 (t, *J*=1.2 Hz, 1H), 7.46-7.48 (m, 1H), 7.55 (d, *J*=8.5 Hz, 1H), 7.59 (s, 1H), 7.61 (d, *J*=15.9 Hz, 1H), 7.63-7.64 (m, 1H), 7.67 (s, 1H), 8.11 (s, 1H), 8.29 (t, *J*=5.6 Hz, 1H), 11.34 (s, 1H); MS (ESI(+)) m/e 443.1 $(M+H)^+$.

Example 293

(2E)-3-[4-amino-3-(1H-indol-5-yl)thieno[3,2-c]pyridin-7-yl]-N-[2-(diethylamino)ethyl]acrylamide

The desired product was prepared by substituting Example 291A for Example 78 in Example 86, then substituting the product for Example 21B in Example 29. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.98 (t, *J*=7.0 Hz, 6H), 2.48-2.55 (m, 6H), 3.23-3.29 (m, 2H), 5.81 (s, 2H), 6.51-6.52 (m, 1H), 6.61 (d, *J*=15.6 Hz, 1H), 7.15 (dd, *J*=8.1, 1.7 Hz, 1H), 7.46-7.48 (m, 1H), 7.54 (d, *J*=8.1 Hz, 1H), 7.58 (d, *J*=15.6 Hz, 1H), 7.58 (s, 1H), 7.63-7.64 (m, 1H), 8.10 (s, 1H), 8.13 (t, *J*=5.4 Hz, 1H), 11.34 (s, 1H); MS (ESI(+)) m/e 434.1 $(M+H)^+$.

Example 294

N-[4-(4-amino-7-iodothieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

Example 294A

tert-butyl 4-(4-aminothieno[3,2-c]pyridin-3-yl)-2-methoxyphenylcarbamate

A solution of Example 1B (1.0g, 4.365 mmol) in ethyleneglycol dimethyl ether (20 mL) was treated with tert-butyl 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (1.83g, 5.238 mmol), $Pd(PPh_3)_4$ (0.303g, 0.262 mmol), and a solution of sodium carbonate (1.11g, 10.473 mmol) in water (10 mL), stirred at 85 °C for 16 hours under nitrogen, concentrated, and treated with dichloromethane. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 100% ethyl acetate to provide 1.62g (100%) of the desired product. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.1 (s, 1H), 7.8 (m, 2H), 7.41 (s, 1H), 7.2 (m, 1H), 7.1 (s, 1H), 7-6.95 (m, 1H), 3.8 (s, 3H), 1.458 (s, 9H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3 μm particle size, 33 x 4.6mm; 70% 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R_t=3.73 min (95%), MS m/e 372.2 $(M+H)^+$.

Example 294B

tert-butyl 4-(4-amino-7-iodothieno[3,2-*c*]pyridin-3-yl)-2-methoxyphenylcarbamate

A solution of Example 294A (1.49g, 4.01 mmol) in dimethylformamide (20 mL) was treated portionwise with N-iodosuccinimide (1.083g, 4.813 mmol), stirred at room temperature for 2 hours, treated with saturated sodium thiosulfate, stirred for 30 minutes, and filtered. The filter cake was washed with water and dried in a vacuum oven to provide 1.884g (94%) of the desired product. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.111 (s, 1H), 8.018 (s, 1H), 7.8 (m, 1H), 7.566 (s, 1H), 7.086–7.082 (m, 1H), 7.0 (m, 1H), 5.6 (s, 2H), 3.841 (s, 3H), 1.478 (s, 9H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70% 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R_t=4.42 min (95%), MS m/e 498.2 $(M+H)^+$.

Example 294C

3-(4-amino-3-methoxyphenyl)-7-iodothieno[3,2-*c*]pyridin-4-amine

A solution of Example 294B (8.641g, 17.374 mmol) in dichloromethane (100 mL) at 0 °C was treated dropwise with trifluoroacetic acid (30 mL) in dichloromethane (20 mL), stirred at 0 °C for 1 hour and at room temperature for 3 hours, concentrated, and dried under high vacuum. The residue was treated with dichloromethane and 6N HCl. The layers were partitioned and the organic layer was extracted with 6N HCl. The combined aqueous layers were cooled to 0 °C. The aqueous layer was basified to pH 11 and the resulting precipitate was collected by filtration to provide 4.787g of the desired product. The filtrate was extracted three times with ethyl acetate and the combined extracts were dried ($MgSO_4$), filtered, and concentrated to provide 2.41g of additional product. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.1 (s, 1H), 7.67 (s, 1H), 6.93 (s, 1H), 6.8 (s, 2H), 6.5 (s, 2H), 3.8 (s, 3H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70% 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R_t=3.25 min (95%), MS m/e 398.0 $(M+H)^+$.

Example 294D

1-methyl-1*H*-indole-2-carbonyl chloride

A suspension of 1-methyl-1H-2-indolecarboxylic acid (0.485g, 2.769 mmol) in dichloromethane (10 mL) at 0 °C was treated with oxalyl chloride (0.369g, 2.91 mmol) and one drop of dimethyl formamide. The reaction mixture was stirred at 0 °C for 1 hour and at room temperature for 2 hours. The solvent was removed under reduced pressure and dried on the high vacuum for 1 hour. The residue was used directly in the subsequent reaction without further purification or analysis.

Example 294E

N-[4-(4-amino-7-iodothieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

A solution of Example 294C (1.0g, 2.517 mmol) in pyridine (10 mL) at 0 °C was treated dropwise with a solution of Example 294D (0.536g, 2.769 mmol) in dichloromethane (5 mL), stirred at 0 °C for 1 hour and at room temperature for 2 hours, treated with 1N NaOH, stirred for 15 minutes, and concentrated. Dichloromethane was added and the layers were partitioned. The aqueous layer was extracted with dichloromethane. The combined organic layers were washed with water, dried ($MgSO_4$), filtered, and concentrated. The solid was dried on the high vacuum to remove residual pyridine to provide 0.906g (65%) of the desired product. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.5 (s, 1H), 8.042-7.993 (m, 2H), 7.72-7.70 (m, 1H), 7.641-7.637 (m, 1H), 7.602-7.581 (m, 1H), 7.337-7.317 (m, 2H), 7.212 (m, 1H), 7.174-7.136 (m, 1H), 7.095-7.075 (m, 1H), 5.673 (s, 2H), 4.043 (s, 3H), 3.916 (s, 3H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70% 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R_t=4.33 min (95%), MS m/e 553.11 $(M-H)^-$.

General Procedure for Sonogashira Couplings

A Milestone® microwave tube was charged with Example 294E (0.050g to 0.065g, ~0.09 mmol), the appropriately functionalized alkyne (0.27 mmol), $Pd(PPh_3)_4$ (0.005g, 0.0045 mmol), cuprous iodide (0.001g, 0.0045 mmol), and piperidine (3 mL). The reaction mixture was stirred at 85 °C under Milestone® microwave conditions for 5 minutes and concentrated. The concentrate was purified by flash chromatography on silica gel or by preparative HPLC. LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70% 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min).

The following compounds were prepared following this procedure using the indicated alkyne.

Example	Final Product	Starting Alkyne	Amt. (mg) (Yield%)	MS m/z

295	N-{4-[4-amino-7-(phenylethynyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	ethynylbenzene	11 (23%)	529.4
296	N-{4-[4-amino-7-(3-amino-3-methyl-1-butynyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	1,1-dimethyl-2-propynylamine	18 (30%)	510.4
297	N-(4-{4-amino-7-[3-(dimethylamino)-1-propynyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide	N,N-dimethyl-N-2-propynylamine	17 (28%)	510.4
298	N-{4-[4-amino-7-(3-hydroxy-3-methyl-1-butynyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	2-methyl-3-butyn-2-ol	27 (45%)	511.4

299	N-{4-[4-amino-7-(2-pyridinylethynyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	2-ethynylpyridine	16 (27%)	530.4
300	N-{4-[4-amino-7-(3-methoxy-1-propynyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	3-methoxy-1-propyne	21 (36%)	497.4
301	*N*-{4-[4-amino-7-(5-hydroxy-1-pentynyl)thieno[3,2-*c*]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-indole-2-carboxamide	4-pentyn-1-ol	22 (37%)	511.4
302	N-(4-{4-amino-7-[(1-aminocyclohexyl)ethynyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide	1-ethynylcyclohexanamine	36 (56%)	533.5
303	5-[4-amino-3-(3-methoxy-4-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}phenyl)thieno[3,2-c]pyridin-7-yl]-4-pentynoic acid	4-pentynoic acid	12 (20%)	525.3

304	N-{4-[4-amino-7-(4-hydroxy-1-butynyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	3-butyn-1-ol	10 (17%)	497.4
305	N-(4-{4-amino-7-[3-(methylamino)-1-propynyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide	N-methyl-N-2-propynylamine	3 (<1%)	496.5
306	N-(4-{4-amino-7-[3-(diethylamino)-1-propynyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide	N,N-diethyl-N-2-propynylamine	34 (54%)	538.6
307	N-{4-[4-amino-7-(3-hydroxy-1-propynyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide (acetate salt)	2-propyn-1-ol	15 (27%)	483.4
308	tert-butyl 3-[4-amino-3-(3-methoxy-4-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}phenyl)thieno[3,2-c]pyridin-7-yl]-2-propynylcarbamate	tert-butyl 2-propynylcarbamate	100 (95%)	582.5
309	tert-butyl 5-{[4-amino-3-(3-methoxy-4-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}phenyl)thieno[3,2-c]pyridin-7-yl]ethynyl}-2-pyridinylcarbamate	tert-butyl 5-ethynyl-2-pyridinylcarbamate	93 (91%)	645.6

Example 310

N-{4-[4-amino-7-(3-amino-1-propynyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-

methyl-1H-indole-2-carboxamide

A solution of Example 308 (0.095g, 0.163 mmol) in dichloromethane (10 mL) at 0 °C was treated with a solution of trifluoroacetic acid (4 mL) in dichloromethane (5 mL). The reaction mixture was stirred at 0 °C for 35 minutes and at room temperature for 15 hours. The solvent was removed under reduced pressure and the residue was dried under high vacuum. Ethyl acetate and 5N NaOH were added. The layers were partitioned and the organic layer was washed with NaOH, dried ($MgSO_4$), filtered and concentrated to provide 0.039g (49%) of the desired product. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.518 (s, 1H), 8.015-7.995 (m, 2H), 7.719-7.699 (m, 1H), 7.632-7.581 (m, 2H), 7.352-7.314 (m, 2H), 7.213 (m, 1H), 7.172-7.15 (m, 1H), 7.134-7.076 (m, 1H), 5.85 (br s, 2H), 4.038 (s, 3H), 3.915 (s, 3H), 3.681 (s, 2H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70% 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R_t=3.12 min (100%), MS m/e 482.5 $(M+H)^+$.

Example 311

N-(4-{4-amino-7-[(6-amino-3-pyridinyl)ethynyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide

A solution of Example 309 (0.080g, 0.12 mmol) in dichloromethane (5 mL) at 0 °C was treated with a solution of trifluoroacetic acid (2 mL) in dichloromethane (5 mL). The reaction mixture was stirred at 0 °C for 35 minutes and at room temperature for 15 hours. The solvent was removed under reduced pressure and the residue was dried under high vacuum. Ethyl acetate and 5N NaOH were added. The layers were partitioned and the organic layer was washed with NaOH, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude material was purified by preparative HPLC to provide 0.003g (1%) of the desired product. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.517 (s, 1H), 8.15-8.146 (m, 1H), 8.06-8.005 (m, 2H), 7.72-7.701 (m, 1H), 7.647 (s, 1H), 7.604-7.583 (m, 1H), 7.554-7.527 (m, 2H), 7.356-7.315 (m, 2H), 7.233 (m, 1H), 7.173-7.091 (m, 2H), 6.494-6.459 (m, 2H), 5.8 (br s, 2H), 4.041 (s, 3H), 3.923 (s, 3H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70% 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R_t=3.65 min (100%), MS m/e 545.5 $(M+H)^+$.

Example 312

N-(4-{4-amino-7-[6-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-hexynyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide

A microwave tube charged with Example 294E (0.100g, 0.18 mmol), 2-(5-hexynyl)-1H-isoindole-1,3(2H)-dione (0.123g, 0.541 mmol), $PdCl_2(PPh_3)_2$ (0.006g, 0.009 mmol),

cuprous chloride (0.002g, 0.009 mmol), triethylamine (0.054g, 0.541 mmol), and DMF (4 mL) was stirred at 85 °C for 5 minutes under microwave conditions and concentrated. The residue was purified by flash chromatography on silica gel using 1:1 ethyl acetate/heptane then 100% ethyl acetate to provide 0.078g (66%) of the desired product ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.479 (s, 1H), 7.988-7.957 (m, 1H), 7.878-7.763 (m, 5H), 7.686-7.666 (m, 1H), 7.57-7.549 (m, 2H), 7.319-7.28 (m, 2H), 7.175-7.171 (m, 1H), 7.139-7.101 (m, 1H), 7.059-7.034 (m, 1H), 5.673 (br s, 2H), 4.006 (s, 3H), 3.882 (s, 3H), 3.654-3.62 (m, 2H), 2.572 (m, 2H), 1.839-1.776 (m, 2H), 1.619-1.546 (m, 2H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70% 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R_t=4.6 min (95%), MS m/e 654.6 $(M+H)^+$.

Example 313

N-{4-[4-amino-7-(3-formyl-2-furyl)-1-benzothien-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

A mixture of Example 294E (0.120g, 0.217 mmol), 3-formyl-2-furylboronic acid (0.033g, 0.236 mmol), $Pd(PPh_3)_4$ (0.012g, 0.010 mmol), and sodium carbonate (0.057g, 0.538 mmol) in DMF (2 mL) and water (1 mL) was heated at 80 °C for 16 hours, cooled to ambient temperature, and concentrated. The residue was partitioned between water (20 mL) and methanol/dichloromethane (1:9, 20 mL). The layers were separated and the aqueous layer was extracted further with methanol/dichloromethane (1:9, 2 x 20 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel deactivated with triethylamine, using methanol/dichloromethane (1:24) as the mobile phase to provide the desired product (0.017g, 0.032 mmol). ^{1}H NMR (DMSO-d_6, 400MHz) δ 9.48 (s, 1H), 7.96 (d, 1H), 7.82 (d, 1H), 7.68 (d, 1H), 7.57 (m, 2H), 7.51 (s, 1H), 7.33 (s, 1H), 7.29 (m, 1H), 7.26 (d, 1H), 7.17 (m, 1H), 7.13 (t, 1H), 7.05 (m, 1H), 4.04 (s, 3H), 3.91 (s, 3H); MS m/e 521 $(M-H)^-$.

Example 314

tert-butyl (2E)-3-[4-amino-3-(3-methoxy-4-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}phenyl)thieno[3,2-c]pyridin-7-yl]-2-propenylcarbamate

Example 314A

tert-butyl allylcarbamate

A solution of copper cyanide (1.15g, 12.9 mmol) in THF (30 mL) at -78 °C was treated slowly with n-butyllithium (16.9 mL, 27.1 mmol), stirred for 15 minutes at -78 °C, treated with tributyltin hydride (7.88g, 7.30 mL, 27.1 mmol) over a period of 5 minutes,

stirred for 15 minutes, treated with tert-butyl 2-propynylcarbamate (2.00g, 12.9 mmol) in tetrahydrofuran (7 mL), stirred at –78 °C for 1 hour, and treated with a 9:1 aqueous solution of ammonium chloride:ammonium hydroxide (250 mL) and dichloromethane (200 mL). The suspension was filtered through a short pad of diatomaceous earth (Celite®). The organic phase of the filtrate was washed with brine and concentrated. The residue was purified on silica gel using 1-2% ethyl acetate/heptane to provide the desired product (3.66g, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (dt, B part of an AB system, J=19.3 Hz, 1.3 Hz, 1H); 5.93 (dt, A part of an AB system, J=19.3 Hz, 4.8 Hz, 1H), 4.59 (br s, 1H), 3.78 (br s, 2H), 1.45 (s, 9H), 1.32-1.26, (m, 12H), 0.90-0.85 (m, 15H).

Example 314B

tert-butyl (2E)-3-[4-amino-3-(3-methoxy-4-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}phenyl)thieno[3,2-c]pyridin-7-yl]-2-propenylcarbamate

A degassed suspension of Example 294E (2.50g, 4.51 mmol), Example 314A (2.62g, 5.87 mmol), and potassium fluoride (0.340g, 5.87 mmol) in toluene (45 mL) was treated with $Pd(PPh_3)_4$ (0.360g, 0.316 mmol), degassed twice more, and then heated to 115 °C for 14 hours. The suspension was cooled to room temperature and the solvent was removed under reduced pressure. The resulting solid was triturated with ethanol/dichloromethane (10:1) (100 mL) and collected by vacuum filtration provide the desired product (2.3g, 90%). LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70% 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min); MS m/e 584.6 $(M+H)^+$, R_t = 4.1 minutes; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.51 (s,1H), 7.99 (d, J=8.0 Hz,1H), 7.95 (s, 1H), 7.70 (d, J=8.0 Hz, 1H), 7.63 (s, 1H), 7.58 (d, J=8.4 Hz, 1H), 7.35 (s, 1H), 7.32 (d, J=8.4 Hz, 1H), 7.21 (d, J=1.5 Hz, 1H), 7.15 (dd, J=7.8 Hz, 7.0 Hz, 1H), 7.08 (dd, J=8.0 Hz, 1.9 Hz, 1H), 6.58 (d, J=16.2 Hz, 1H), 6.21 (td, J=16.2 Hz, J=5.5 Hz, 1H), 5.65 (br s, 1H), 4.04 (s, 3H), 3.91 (s, 3H), 3.80 (br m, 2H), 1.42 (s, 9H).

Example 315

N-(4-{4-amino-7-[(1E)-3-amino-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide

A suspension of Example 314B (0.625g, 1.07 mmol) in dichloromethane (9 mL) at 0 °C was treated with a solution of trifluoroacetic acid (2.4g, 21.4 mmol) in dichloromethane (2 mL). The solution was slowly warmed to room temperature, stirred for 4 hours, and concentrated. The resulting trifluoroacetate salt was treated with 50% NaOH and extracted with 10:1 dichloromethane/methanol (4 x 200 mL). The solvents were removed under reduced pressure to provide the crude product which was purified by silica gel chromatography using 10% methanol/dichloromethane to 25% methanol (with 2.5%

ammonium hydroxide)/dichloromethane to provide the desired product (0.330g, 58%): LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70% 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min); MS m/e 484.6 $(M+H)^+$; R_t = 3.0 minutes; ^1H NMR (DMSO-d_6, 400 MHz) δ 9.50 (s, 1H), 7.98 (d, *J*=8.0 Hz, 1H), 7.94 (s, 1H), 7.69 (d, *J*=7.8 Hz, 1H), 7.62 (s, 1H), 7.58 (d, *J*=8.6 Hz, 1H), 7.34 (s, 1H), 7.31 (d, *J*=7.2 Hz, 1H), 7.20 (d, *J*=1.9 Hz, 1H), 7.14 (dd, *J*=7.8 Hz, 8.0 Hz, 1H), 7.08 (dd, *J*=8.2 Hz, 1.9 Hz, 1H), 6.67 (d, *J*=16.2 Hz, 1H), 6.33 (td, *J*=16.2 Hz, 5.5 Hz, 1H), 5.60 (br s, 1H), 4.03 (s, 3H), 3.91 (s, 3H), 3.44 (dd, *J*=5.6 Hz, 1.3 Hz, 2H).

General Procedure for Reductive Amination with Example 315

A suspension of Example 315 (0.050g, 0.104 mmol) and the appropriate ketone/aldehyde (0.087 mmol) in dichloroethane (1.5 mL) was treated with sodium triacetoxyborohydride (0.036g, 0.173 mmol), stirred at room temperature for 2-12 hours, treated with 10% NaOH (3 mL) and dichloromethane (3 mL), stirred for 15 minutes, filtered through an Empore® cartridge, and concentrated. The crude product was purified in one of three ways: Method A: Triturated in ethanol and collected by filtration. Method B: Purified by preparative reverse phase HPLC (Rainin C18, 8 mm, 300 Å, 25 cm; 40% acetonitrile - 0.1M ammonium acetate isocratic for 5 minutes, then 40-100% acetonitrile/0.1M ammonium acetate over 30 min, 21 mL/min) followed by lyophilization. Method C: Purified by reverse phase HPLC (Rainin C18, 8 mm, 300 Å, 25 cm; 40% acetonitrile - 0.1M ammonium acetate isocratic for 5 minutes, then 5 -100% acetonitrile/0.1M ammonium acetate over 30 min, 21 mL/min) then lyophilized. LCMS conditions: LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70% 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min).

The following examples were prepared by this procedure using the indicated ketone or aldehyde.

Example	Final Product	Starting Ketone/Aldehyde	Yield%	MS m/e
316	N-[4-(7-{(1E)-3-[(1-acetyl-4-piperidinyl)amino]-1-propenyl}-4-aminothieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide	1-acetyl-4-piperidinone	25	609.5
317	N-(4-{4-amino-7-[(1E)-3-(tetrahydro-2H-pyran-4-ylamino)-	tetrahydro-4*H*-pyran-4-one	31	568.1

	1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide (acetate salt)			
318	N-(4-{4-amino-7-[(1E)-3-(1,4-dioxaspiro[4.5]dec-8-ylamino)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide	1,4-dioxaspiro[4.5]decan-8-one	48	624.3
319	N-[4-(4-amino-7-{(1E)-3-[(3,3-dimethyl-1,5-dioxaspiro[5.5]undec-9-yl)amino]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide (acetate salt)	3,3-dimethyl-1,5-dioxaspiro[5.5]undecan-9-one	50	666.3
320	N-{4-[4-amino-7-((1E)-3-{[(6-methyl-2-pyridinyl)methyl]amino}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide (acetate salt)	6-methyl-2-pyridinecarbaldehyde	10	589.5
321	N-{4-[4-amino-7-((1E)-3-{[2,3-dihydroxypropyl]amino}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	2,3-dihydroxypropanal	2	558.1
322	N-[4-(4-amino-7-{(1E)-3-[(1-isopropyl-4-piperidinyl)amino]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide	1-isopropyl-4-piperidinone	25	609.7

Purification Methods and Spectral Data

Example 316

Purification Method: A; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.01-7.99 (m, 2H), 7.70 (d, *J*=7.4 Hz, 1H), 7.66 (s, 1H), 7.58 (d, *J*=8.2 Hz, 1H), 7.35 (s, 1H), 7.32 (d, *J*=7.4 Hz, 1H), 7.20 (d, *J*=1.9 Hz, 1H), 7.15 (dd, *J*=7.6 Hz, 8.0 Hz, 1H), 7.08 (dd, *J*=6.5 Hz, 1.9 Hz, 1H), 6.89 (d (br), 1H), 6.27 (td, *J*=16.0 Hz, 6.2 Hz, 1H), 5.76 (br s, 1H), 4.04 (s, 3H), 3.91 (s, 3H), 3.70 (m, 2H), 3.07 (m, 2H), 2.62 (m, 2H), 2.01 (s, m, 4H), missing signals for 4 aliphatic protons that are under residual solvent and water signals.

Example 317

Purification Method: B; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.00 (t, *J*=8.0 Hz, 1H), 7.70 (d, *J*=7.70 Hz, 1H), 7.62 (s, 1H), 7.58 (d, *J*=8.6 Hz, 1H), 7.34 (s, 1H), 7.31 (d, *J*=7.2 Hz, 1H), 7.19 (d, *J*=1.9 Hz, 1H), 7.14 (t, *J*=7.2 Hz, 1H), 7.08 (dd, *J*=8.0 Hz, 1.8 Hz, 1H), 6.68 (d, *J*=16.4 Hz, 1H), 6.28 (td, *J*=16.2 Hz, 6.2 Hz, 1H), 5.62 (br s, 1H), 4.04 (s, 3H), 3.91 (s, 3H), 3.84 (m, 2H), 3.45 (m, 2H), 3.27 (m, 2H), 2.32 (m, 1H), 1.86 (m, 2H), 1.30 (m, 2H), 1.91 (s, 3H, acetate).

Example 318

Purification Method: B; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 7.99 (d, *J*=8.0 Hz, 1H), 7.93 (s, 1H), 7.69 (d, *J*=7.8 Hz, 1H), 7.61 (s, 1H), 7.58 (d, *J*=7.6 Hz, 1H), 7.34 (s, 1H), 7.31 (d, *J*=8.4 Hz, 1H), 7.20 (d, *J*=1.8 Hz, 1H), 7.14 (dd, *J*=8.0 Hz, 7.2 Hz, 1H), 7.07 (dd, *J*=7.6 Hz, 1.9 Hz, 1H), 6.65 (d, *J*=16.0 Hz, 1H), 6.28 (td, *J*=16.2 Hz, 6.0 Hz, 1H), 5.60 (br s, 1H), 4.04 (s, 3H), 3.91 (s, 3H), 3.84 (m, 4H), 3.39 (m, 2H), 2.54 (m, 1H), 1.79 (m, 2H), 1.68 (m, 2H), 1.48-1.34 (m, 4H).

Example 319

Purification Method: C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 7.99 (dd, (*J*=8.0 Hz, 8.2 Hz, 1H), 7.93 (s, 1H), 7.69 (d, *J*=8.2 Hz,1H), 7.61 (s, 1H), 7.57 (d, *J*=8.4 Hz, 1H), 7.34 (s, 1H), 7.31 (d, *J*=7.2 Hz,1H), 7.20 (d, *J*=1.8 Hz, 1H), 7.14 (dd, *J*=8.0 Hz, 7.8 Hz, 1H), 7.07 (dd, *J*=8.0 Hz, 1.8 Hz, 1H), 6.65 (d, *J*=16.1 Hz, 1H), 6.27 (td, *J*=16.2 Hz, 6.0 Hz, 1H), 5.59 (br s, 1H), 4.03 (s, 3H), 3.91 (s, 3H), 3.42-3.39 (m, 6H), 2.32 (m, 1H), 2.08 (m, 2H), 1.71 (m, 2H), 1.38-1.22 (m, 4H), 0.886 (s, 6H), 1.89 (s, 3H, acetate).

Example 320

Purification Method: C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.50 (s, 1H), 7.99 (dd, *J*=8.2 Hz, 7.8 Hz, 1H), 7.96 (s, 1H), 7.70-7.67 (m, 2H), 7.63 (s, 1H), 7.58 (d, *J*=8.4 Hz, 1H), 7.34 (s, 1H), 7.31 (d, *J*=8.2 Hz, 1H), 7.27 (d, *J*=7.4 Hz, 1H), 7.19 (d, *J*=1.9 Hz, 1H), 7.15 – 7.12 (m, 2H), 7.07 (dd, *J*=7.8 Hz, 1.8 Hz, 1H), 6.73 (d (br), *J*=16.0 Hz, 1H), 6.30 (td, *J*=16.0 Hz, 6.0 Hz, 1H), 4.03 (s, 3H), 3.91 (s, 3H), 3.54 (br s, 2H), 2.47 (s, 3H), 2.33 (m, 2H), 1.90

(s, 3H, acetate).

Example 321

Purification Method: C; ^{1}H NMR too dilute for definitive analysis. Analytical HPLC (Rainin C18, 8 mm, 300 Å, 25 cm; 5 -100% acetonitrile over 15 minutes then isocratic 5 minutes – 1.0 mL/min): R_t = 11.9 minutes.

Example 322

Purification Method: A; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.00 (dd, *J*=8.2 Hz, 8.0 Hz, 1H), 7.94 (s, 1H), 7.70 (d, *J*=8.0 Hz, 1H), 7.61 (s, 1H), 7.59 (d, *J*=8.0 Hz, 1H), 7.35 (s, 1H), 7.32 (d, *J*=7.4 Hz, 1H), 7.20 (d, *J*=1.8 Hz, 1H), 7.15 (t, *J*=7.6 Hz, 1H), 7.08 (dd, *J*=8.2 Hz, 1.8 Hz, 1H), 6.65 (d, *J*=16.2 Hz, 1H), 6.28 (td, *J*=16.2 Hz, 6.0 Hz, 1H), 5.59 (br s, 1H), 4.04 (s, 3H), 3.91 (s, 3H), 3.39 (m, 2H), 2.74 (m, 2H), 2.65 (m, 1H), 2.40 (m, 1H), 2.08 (m, 2H), 1.84 (m, 2H), 1.27-1.17 (m, 2H), 0.940 (d, 6H).

General Procedure for Reductive Aminations with Example 176C

A mixture of Example 176C (40 mg, 0.083 mmol), sodium triacetoxyborohydride (35 mg, 0.166 mmol) and the appropriate amine (0166 mmol) in 1,2-dichloromethane (2 mL) was stirred for 2 to 72 hours at ambient temperature. The mixture was concentrated and the residue was purified by normal or reverse phase chromatography. Where necessary a Boc-protected diamine was used for the reductive amination then the protecting group was removed by stirring the reaction mixture in a 2:1 mixture of acetone and 6N hydrochloric acid for 2 hours followed by concentration and purification of the residue.

The following examples were prepared by this general method using the indicated amines:

Example 323

N-{4-[4-amino-7-((1E)-3-{4-[2-(dimethylamino)ethyl]-1-piperazinyl}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

Prepared as the diacetate salt from N,N-dimethyl-N-[2-(1-piperazinyl)ethyl]amine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.50 (s, 1H), 8.00 (d, 1H), 7.96 (s, 1H), 7.69 (d, 1H), 7.61 (s, 1H), 7.59 (d, 1H), 7.34 (s, 1H), 7.33 (d, 1H), 7.19 (s, 1H), 7.15 (t, 1H), 7.07 (d, 1H), 6.66 (d, 1H), 6.21 (m, 1H), 5.63 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.16 d, 2H), 2.2-2.5 (m, 12H), 2.13 (s, 6H), 1.87 (s, 6H); MS m/e 624.5 $(M+H)^+$, 622.6 $(M-H)^-$.

Example 324

N-[4-(4-amino-7-{(1E)-3-[4-(2-methoxyethyl)-1-piperazinyl]-1-propenyl}thieno[3,2-

c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

Prepared from 1-(2-methoxyethyl)piperazine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.49 (s, 1H), 7.99 (d, 1H), 7.95 (s, 1H), 7.69 (d, 1H), 7.60 (s, 1H), 7.57 (d, 1H), 7.34 (s, 1H), 7.31 (d, 1H), 7.19 (s, 1H), 7.14 (t, 1H), 7.06 (d, 1H), 6.66 (d, 1H), 6.20 (m, 1H), 5.62 (br s, 2H), 4.03 (s, 3H), 3.90 (s, 1H), 3.41 (t, 2H), 3.22 (s, 3H), 3.16 (d, 2H), 2.3-2.5 (m, 10H), MS m/e 611.5 $(M+H)^+$.

Example 325

N-{4-[4-amino-7-((1E)-3-{4-[3-(dimethylamino)propyl]-1-piperazinyl}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

Prepared as the triacetate salt from N,N-dimethyl-N-[3-(1-piperazinyl)propyl]amine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.50 (s, 1H), 7.99 (d, 1H), 7.96 (s, 1H), 7.69 (d, 1H), 7.60 (s, 1H), 7.58 (d, 1H), 7.35 (s, 1H), 7.32 (t, 1H), 7.20 (s, 1H), 7.14 (t, 1H), 7.06 (d, 1H), 6.65 (d, 1H), 6.21 (m, 1H), 5.62 (br s, 1H), 4.03 (s, 3H), 3.90 (s, 3H), 3.16 (d, 2H), 2.39 (m, 8H), 2.26 (t, 2H), 2.19 (m, 2H), 2.09 (s, 6H), 1.85 (s, 9H), 1.53 (m, 2H); MS m/e 638.8 $(M+H)^+$, 636.7 $(M-H)^-$.

Example 326

N-{4-[4-amino-7-((1E)-3-{4-[(2-pyrimidinylamino)methyl]-1-piperidinyl}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

Prepared as the acetate salt from N-(4-piperidinylmethyl)-2-pyrimidinamine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.50 (s, 1H), 8.00 (d, 1H), 7.96 (s, 1H), 7.71 (d, 1H), 7.61 (s, 1H), 7.32 (t, 1H), 7.19 (s, 2H), 7.15 (t, 1H), 7.07 (d, 1H), 6.65 (d, 1H), 6.51 (t, 1H), 6.22 (m, 1H), 5.63 (br s, 2H), 4.03 (s, 3H), 3.91 (s, 3H), 3.15 (d, 2H), 2.91 (d, 2H), 2.63 (m, 2H), 1.6-2.0 (m, 12H); MS m/e 659.5 $(M+H)^+$, 657.5 $(M-H)^-$.

Example 327

N-[4-(4-amino-7-{(1E)-3-[4-(aminocarbonyl)-1-piperidinyl]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

Prepared as the diacetate salt from 4-piperidinecarboxamide. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.50 (s, 1H), 8.00 (d, 1H), 7.97 (s, 1H), 7.70 (d, 1H), 7.62 (s, 1H), 7.58 (d, 1H), 7.35 (s, 1H), 7.33 (t, 1H), 7.21 (m, 2H), 7.15 (t, 1H), 7.07 (d, 1H), 6.74 (s, 1H), 6.66 (d, 1H), 6.24 (m, 1H), 5.63 (br s, 2H), 4.04 (s, 3H), 3.92 (s, 3H), 3.16 (d, 2H), 2.95 (m, 1H), 1.85-2.09 (m, 4H), 1.89 (s, 6H), 1.53-1.74 (m, 4H); MS m/e 595.5 $(M+H)^+$, 593.2 $(M-H)^-$.

Example 328

N-[4-(4-amino-7-{(1E)-3-[[3-(dimethylamino)propyl](methyl)amino]-1-propenyl}thieno[3,2-

c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

Prepared as the diacetate salt from N,N,N'-trimethyl-1,3-propanediamine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.50 (s, 1H), 8.00 (d, 1H), 7.96 (s, 1H), 7.71 (d, 1H), 7.61 (s, 1H), 7.59 (d, 1H), 7.35 (s, 1H), 7.32 (t, 1H), 7.19 (s, 1H), 7.14 (t, 1H), 7.07 (d, 1H), 6.67 (d, 1H), 6.23 (m, 1H), 5.63 (br s, 2H), 4.03 (s, 3H), 3.91 (s, 3H), 3.19 (d, 2H), 2.38 (t, 2H), 2.23 (t, 2H), 2.20 (s, 3H), 2.11 (s, 6H), 1.86 (s, 6H), 1.58 (m, 2H); MS m/e 583.0 $(M+H)^+$, 581.3 $(M-H)^-$.

Example 329

N-(4-{4-amino-7-[(1E)-3-(4-piperidinylamino)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide

Prepared as the triacetate salt from tert-butyl 4-amino-1-piperidinecarboxylate and deprotected. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.50 (s, 1H), 7.98 (d, 1H), 7.94 (s, 1H), 7.69 (d, 1H), 7.60 (s, 1H), 7.57 (d, 1H), 7.34 (s, 1H), 7.32 (t, 1H), 7.19 (s, 1H), 7.14 (t, 1H), 7.08 (d, 1H), 6.67 (d, 1H), 6.28 (m, 1H), 5.61 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.41 (d, 2H), 3.02 (m, 1H), 2.59 (m, 4H), 1.89 (s, 9H), 1.85 (m, 2H), 1.32 (m, 2H); MS m/e 567.0 $(M+H)^+$, 565.3 $(M-H)^-$.

Example 330

N-[4-(4-amino-7-{(1E)-3-[4-(aminomethyl)-1-piperidinyl]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

Prepared as the tetraacetate salt from tert-butyl 4-piperidinylmethylcarbamate and deprotected. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.51 (s, 1H), 7.99 (d, 1H), 7.96 (s, 1H), 7.69 (d, 1H), 7.61 (s, 1H), 7.58 (d, 1H), 7.35 (s, 1H), 7.33 (t, 1H), 7.19 (d, 1H), 7.14 (t, 1H), 7.06 (dd, 1H), 6.66 (d, 1H), 6.22 (m, 1H), 5.65 (br s, 2H), 4.03 (s, 3H), 3.91 (s, 3H), 3.16 (d, 2H), 2.94 (m, 2H), 2.64 (d, 2H), 1.94 (m, 2H), 1.87 (s, 12H), 1.72 (m, 2H), 1.50 (m, 1H), 1.20 (m, 2H); MS m/e 581.5 $(M+H)^+$, 579.5 $(M-H)^-$.

Example 331

1-{(2E)-3-[4-amino-3-(3-methoxy-4-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}phenyl)thieno[3,2-c]pyridin-7-yl]-2-propenyl}-4-piperidinecarboxylic acid

Prepared as the diacetate salt from 4-piperidinecarboxylic acid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.52 (s, 1H), 8.00 (d, 1H), 7.97 (s, 1H), 7.72 (d, 1H), 7.61 (s, 1H), 7.59 (d, 1H), 7.35 (s, 1H), 7.33 (m, 1H), 7.20 (s, 1H), 7.15 (t, 1H), 7.07 (d, 1H), 6.67 (d, 1H), 6.24 (m, 1H), 5.65 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.16 (d, 2H), 2.86 (m, 2H), 2.15 (m, 1H), 2.02 (m, 2H), 1.88 (s, 6H), 1.80 (m, 2H), 1.57 (m, 2H); MS m/e 596.5 $(M+H)^+$, 594.5 $(M-H)^-$.

Example 332

N-[4-(4-amino-7-{(1E)-3-[(4-aminocyclohexyl)amino]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

Prepared as the triacetate salt from tert-butyl 4-aminocyclohexylcarbamate and deprotected. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.52 (s, 1H), 7.98 (d, 1H), 7.94 (s, 1H), 7.70 (d, 1H), 7.62 (s, 1H), 7.59 (m, 1H), 7.35 (s, 1H), 7.33 (m, 1H), 7.20 (s, 1H), 7.15 (t, 1H), 7.09 (d, 1H), 6.66 (d, 1H), 6.29 (m, 1H), 5.62 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.42 (d, 2H), 2.76 (m, 1H), 2.40 (m, 1H), 1.89 (m, 4H), 1.83 (s, 9H), 1.03-1.28 (m, 4H); MS m/e 681.6 $(M+H)^+$, 679.6 $(M-H)^-$.

Example 333

N-[4-(4-amino-7-{(1E)-3-[methyl(1-methyl-4-piperidinyl)amino]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

Prepared as the tetraacetate salt from N,1-dimethyl-4-piperidinamine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.52 (s, 1H), 7.99 (d, 1H), 7.95 (s, 1H), 7.70 (d, 1H), 7.61 (s, 1H), 7.59 (d, 1H), 7.35 (s, 1H), 7.33 (t, 1H), 7.20 (s, 1H), 7.15 (t, 1H), 7.08 (d, 1H), 6.67 (d, 1H), 6.22 (m, 1H), 5.63 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.29 (d, 2H), 2.82 (m, 2H), 2.36 (m, 1H), 2.21 (s, 3H), 2.13 (s, 3H), 1.84 (s, 12H), 1.82 (m, 2H), 1.73 (m, 2H), 1.49 (m, 2H); MS m/e 595.5 $(M+H)^+$, 593.6 $(M-H)^-$.

Example 334

N-[4-(4-amino-7-{(1E)-3-[4-(6-oxo-1,6-dihydro-2-pyridinyl)-1-piperazinyl]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

Prepared as the acetate salt from 6-(1-piperazinyl)-2(1H)-pyridinone. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.53 (s, 1H), 7.99 (m, 2H), 7.71 (d, 1H), 7.62 (s, 1H), 7.58 (d, 1H), 7.33 (m, 3H), 7.20 (m, 1H), 7.15 (t, 1H), 7.08 (m, 1H), 6.72 (d, 1H), 6.27 (m, 1H), 6.05 (d, 1H), 5.85 (d, 1H), 5.67 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.39 (m, 4H), 3.23 (d, 2H), 2.53 (m, 4H), 1.89 (s, 3H); MS m/e 646.6.6 $(M+H)^+$, 644.7$(M-H)^-$.

Example 335

N-(4-{4-amino-7-[(1E)-3-(4-methyl-1,4-diazepan-1-yl)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide

Prepared as the acetate salt from 1-methyl-1,4-diazepane. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.52 (s, 1H), 8.00 (d, 1H), 7.96 (s, 1H), 7.72 (d, 1H), 7.61 (s, 1H), 7.58 (d, 1H), 7.35 (s, 1H), 7.33 (t, 1H), 7.19 (s, 1H), 7.15 (t, 1H), 7.07 (d, 1H), 6.67 (d, 1H), 6.24 (m, 1H), 5.64 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.29 (d, 2H), 2.68 (m, 4H), 2.56 (m, 4H), 2.25 (s, 3H),

1.86 (s, 3H), 1.73 (m, 2H); MS m/e 581.5 $(M+H)^+$, 579.4 $(M-H)^-$.

Example 336

N-[4-(4-amino-7-{(1E)-3-[4-(2-pyrazinyl)-1-piperazinyl]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

Prepared from 2-(1-piperazinyl)pyrazine. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.52 (s, 1H), 8.33 (d, 1H), 8.08 (m, 1H), 8.01 (d, 1H), 7.99 (s, 1H), 7.84 (d, 1H), 7.72 (d, 1H), 7.62 (s, 1H), 7.59 (d, 1H), 7.33 (m, 2H), 7.20 (m, 1H), 7.15 (t, 1H), 7.08 (dd, 1H), 6.73 (d, 1H), 6.28 (m, 1H), 5.67 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.59 (m, 4H), 3.25 (d, 2H), 2.56 (m, 4H); MS m/e 631.6 $(M+H)^+$.

Example 337

N-{4-[4-amino-7-((1E)-3-{[2-(2-hydroxyethoxy)ethyl]amino}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

Prepared as the diacetate salt from 2-(2-aminoethoxy)ethanol. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.51 (s, 1H), 8.00 (d, 1H), 7.95 (s, 1H), 7.70 (d, 1H), 7.58-7.62 (m, 2H), 7.07-7.35 (m, 5H), 6.70 (d, 1H), 6.30 (dt, 1H), 5.62 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.40-3.53 (m, 8H), 2.73 (t, 2H), 1.87 (s, 6H); reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=10.2 min; MS m/e 570.5 $(M+H)^+$.

Example 338

N-(4-{4-amino-7-[(1E)-3-({2-[bis(2-hydroxyethyl)amino]ethyl}amino)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide

Prepared as the diacetate salt from 2-[(2-aminoethyl)(2-hydroxyethyl)amino]ethanol. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.51 (s, 1H), 8.00 (d, 1H), 7.95 (s, 1H), 7.70 (d, 1H), 7.58-7.62 (m, 2H), 7.07-7.35 (m, 5H), 6.70 (d, 1H), 6.30 (dt, 1H), 5.62 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.39-3.44 (m, 6H), 2.53-2.61 (m, 8H), 1.87 (s, 6H); reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=10.0 min; MS m/e 613.5 $(M+H)^+$.

Example 339

N-{4-[4-amino-7-((1E)-3-{[2-(4-piperidinyl)ethyl]amino}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

Prepared as the trihydrochloride salt from tert-butyl 4-(2-aminoethyl)-1-piperidinecarboxylate and deprotected. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.49 (s, 1H), 8.15 (m, 2H), 8.01 (s, 1H), 7.71 (d, 1H), 7.60 (d, 1H), 6.98-7.35 (m, 6H), 6.55 (m, 1H), 4.04 (s,

3H), 3.93 (s, 3H), 3.84 (m, 2H), 2.27 (d, 2H), 2.89 (m, 4H), 2.07 (m, 1H), 1.28-1.46 (m, 4H); reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=12.6 min; MS m/e 679.6 $(M-H)^-$.

Example 340

N-{4-[4-amino-7-((1E)-3-{[2-(4-pyridinyl)ethyl]amino}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

Prepared as the acetate salt from 2-(4-pyridinyl)ethanamine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.51 (s, 1H), 8.46 (s, 2H), 8.00 (d, 1H), 7.94 (s, 1H), 7.71 (d, 1H), 7.58-7.62 (m, 3H), 7.08-7.35 (m, 6H), 6.65 (d, 1H), 6.27 (dt, 1H), 5.62 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 2.81 (dt, 4H), 1.87 (s, 3H); reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=10.4 min; MS m/e 587.5 $(M-H)^-$.

Example 341

N-[4-(4-amino-7-{(1E)-3-[4-(2-cyanoethyl)-1-piperazinyl]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

Prepared as the acetate salt from 3-(1-piperazinyl)propanenitrile. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.51 (s, 1H), 8.00 (d, 1H), 7.97 (s, 1H), 7.70 (d, 1H), 7.58-7.62 (m, 2H), 7.07-7.35 (m, 5H), 6.70 (d, 1H), 6.25 (dt, 1H), 5.65 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.34 (t, 2H), 3.19 (br s, 2H), 2.68 (t, 2H), 2.57 (t, 2H), 1.91 (s, 3H); reverse phase HPLC (25% to 100% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=9.9 min; MS m/e 604.5 $(M-H)^-$.

Example 342

N-(4-{4-amino-7-[(1E)-3-(4-amino-1-piperidinyl)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide

Prepared as the diacetate salt from tert-butyl 4-piperidinylcarbamate and deprotected. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.51 (s, 1H), 8.00 (d, 1H), 7.98 (s, 1H), 7.70 (d, 1H), 7.58-7.62 (m, 2H), 7.07-7.35 (m, 5H), 6.70 (d, 1H), 6.25 (dt, 1H), 5.65 (br s, 2H), 4.04 (s, 3H), 3.92 (s, 3H), 3.20 (d, 2H), 2.82-2.95 (m, 3H), 2.03 (t, 2H), 1.91 (s, 3H), 1.85 (d, 2H), 1.50 (q, 2H); reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=11.3 min; MS m/e 565.5 $(M-H)^-$.

Example 343

N-[4-(4-amino-7-{(1E)-3-[4-(3-amino-3-oxopropyl)-1-piperazinyl]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

Prepared as the diacetate salt from 3-(1-piperazinyl)propanamide. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.52 (s, 1H), 8.00 (d, 1H), 7.97 (s, 1H), 7.71 (d, 1H), 7.58-7.62 (m, 2H), 7.07-7.38 (m, 6H), 6.80 (d, 1H), 6.23 (dt, 1H), 5.65 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.17 (d, 2H), 2.49 (br s, 2H), 2.21 (t, 2H), 1.88 (s, 6H); reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=9.7 min; MS m/e 622.7 $(M-H)^-$.

Example 344

N-(4-{4-amino-7-[(1E)-3-(3-oxo-1-piperazinyl)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide

Prepared as the acetate salt from 2-piperazinone. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.52 (s, 1H), 7.99-8.01 (m, 2H), 7.97 (s, 1H), 7.71 (d, 1H), 7.58-7.63 (m, 2H), 7.07-7.38 (m, 5H), 6.71 (d, 1H), 6.23 (dt, 1H), 5.65 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.13-3.26 (m, 4H), 2.63 (m, 2H), 1.87 (s, 3H); reverse phase HPLC (5% to 95% acetonitrile over 25 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=18.9 min; MS m/e 567.5 $(M+H)^+$.

Example 345

N-[4-(4-amino-7-{(1E)-3-[(2-furylmethyl)(methyl)amino]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

Prepared as the acetate salt from N-(2-furylmethyl)-N-methylamine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.52 (s, 1H), 7.99-8.01 (m, 2H), 7.72 (d, 1H), 7.58-7.63 (m, 2H), 7.07-7.38 (m, 5H), 6.71 (d, 1H), 6.23-6.45 (m, 3H), 5.65 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.6 (s, 2H), 3.22 (d, 2H), 2.21 (s, 3H), 1.91 (s, 3H); reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=13.5 min; MS m/e 578.3 $(M+H)^+$.

Example 346

N-[4-(4-amino-7-{(1E)-3-[4-(2-furoyl)-1-piperazinyl]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

Prepared from 1-(2-furoyl)piperazine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.52 (s, 1H), 7.99-8.01 (m, 2H), 7.84 (s, 1H), 7.70 (d, 1H), 7.58-7.63 (m, 2H), 6.99-7.38 (m, 6H), 6.62-6.73 (m, 2H), 6.23 (dt, 1H), 5.65 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.70 (br s, 4H), 3.24 (d, 2H); reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=12.7 min; MS m/e 645.4 $(M-H)^-$.

Example 347

N-{4-[4-amino-7-((1E)-3-{4-[2-(4-morpholinyl)ethyl]-1-piperazinyl}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

Prepared as the acetate salt from 4-[2-(1-piperazinyl)ethyl]morpholine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.52 (s, 1H), 8.00 (d, 1H), 7.99 (s, 1H), 7.71 (d, 1H), 7.58-7.62 (m, 2H), 7.07-7.36 (m, 5H), 6.67 (d, 1H), 6.22 (dt, 1H), 5.65 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.54 (t, 4H), 3.16 (d, 2H), 2.37-2.50 (m, 16H), 1.86 (s, 6H); reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=17.1 min; MS m/e 664.7 $(M-H)^-$.

Example 348

N-{4-[4-amino-7-((1E)-3-{4-[3-(diethylamino)propyl]-1-piperazinyl}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

Prepared as the triacetate salt from N,N-diethyl-N-[3-(1-piperazinyl)propyl]amine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.52 (s, 1H), 8.01 (d, 1H), 7.96 (s, 1H), 7.71 (d, 1H), 7.58-7.62 (m, 2H), 7.07-7.36 (m, 5H), 6.67 (d, 1H), 6.23 (dt, 1H), 5.64 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.16 (d, 2H), 2.35-2.45 (m, 10H), 2.27 (t, 2H), 1.86 (s, 9H), 1.74 (m, 2H), 0.94 (t, 6H); reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=9.9 min; MS m/e 664.6 $(M-H)^-$.

Example 349

N-[4-(4-amino-7-{(1E)-3-[4-(1-methyl-4-piperidinyl)-1-piperazinyl]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

Prepared as the tetraacetate from 1-(1-methyl-4-piperidinyl)piperazine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.52 (s, 1H), 8.01 (d, 1H), 7.96 (s, 1H), 7.71 (d, 1H), 7.58-7.62 (m, 2H), 7.07-7.36 (m, 5H), 6.67 (d, 1H), 6.22 (dt, 1H), 5.64 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.16 (d, 2H), 2.79 (d, 2H), 2.12 (s, 3H), 2.08 (m, 1H), 1.85 (s, 12H), 1.68-1.72 (m, 2H), 1.37-1.40 (m, 2H); reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=9.4 min; MS m/e 648.7 $(M-H)^-$.

Example 350

N-{4-[4-amino-7-((1E)-3-{4-[2-(1-piperidinyl)ethyl]-1-piperazinyl}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

Prepared as the triacetate from 1-[2-(1-piperidinyl)ethyl]piperazine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.52 (s, 1H), 8.01 (d, 1H), 7.97 (s, 1H), 7.71 (d, 1H), 7.58-7.62 (m, 2H), 7.07-7.35 (m, 5H), 6.68 (d, 1H), 6.22 (dt, 1H), 5.64 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.16 (d, 2H), 2.32-2.41 (m, 14H), 1.85 (s, 9H), 1.48 (m, 4H), 1.35 (m, 2H); reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18,

5 μm, 250 x 4.6 column) R_t=9.9 min; MS m/e 664.7 $(M-H)^-$.

Example 351

N-{4-[4-amino-7-((1E)-3-{4-[2-(2-thienyl)ethyl]-1-piperazinyl}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

Prepared from 1-[2-(2-thienyl)ethyl]piperazine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.52 (s, 1H), 8.00 (d, 1H), 7.98 (s, 1H), 7.58-7.72 (m, 4H), 7.29-7.35 (m, 3H), 7.07-7.20 (m, 3H), 6.40-6.90 (m, 2H), 6.70 (d, 1H), 6.24 (dt, 1H), 5.64 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.20 (d, 2H), 2.96 (t, 2H), 2.50-2.57 (m, 10H), 2.65-2.76 (m, 3H), 2.28-2.50 (m, 2H), 2.10 (s, 6H), 1.85 (s, 12H), 1.59-1.65 (m, 1H); reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=13.0 min; MS m/e 661.6 $(M-H)^-$.

Example 352

N-{4-[4-amino-7-((1E)-3-{4-[(2R)-tetrahydro-2-furanylmethyl]-1-piperazinyl}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

Prepared as the diacetate salt from 1-[(2R)-tetrahydro-2-furanylmethyl]piperazine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.52 (s, 1H), 8.00 (d, 1H), 7.97 (s, 1H), 7.71 (d, 1H), 7.58-7.62 (m, 2H), 7.07-7.36 (m, 5H), 6.68 (d, 1H), 6.23 (dt, 1H), 5.64 (br s, 2H), 4.04 (s, 3H), 3.91 (m, 4H), 3.56-3.73 (dq, 2H), 3.16 (d, 2H), 2.35-2.50 (m, 7H), 1.89 (m, 8H), 1.72-1.80 (m, 2H), 1.41-1.49 (m, 1H); reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=20.0 min; MS m/e 635.5 $(M-H)^-$.

Example 353

N-{4-[4-amino-7-((1E)-3-{[3-(4-methyl-1-piperazinyl)propyl]amino}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

Prepared as the tetraacetate salt from 3-(4-methyl-1-piperazinyl)-1-propanamine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.52 (s, 1H), 8.00 (d, 1H), 7.96 (s, 1H), 7.71 (d, 1H), 7.58-7.62 (m, 2H), 7.07-7.36 (m, 5H), 6.70 (d, 1H), 6.28 (dt, 1H), 5.64 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.42 (d, 2H), 2.62 (t, 2H), 2.32-2.34 (m, 8H), 2.30 (s, 3H), 1.83 (s, 12H), 1.60 (m, 2H); reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=9.0 min; MS m/e 666.2 $(M+H+CH_3CN)^+$.

Example 354

N-{4-[4-amino-7-((1E)-3-{4-[3-(4-morpholinyl)propyl]-1-piperazinyl}-1-

propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

Prepared from 4-[3-(1-piperazinyl)propyl]morpholine as the tetraacetate salt. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.52 (s, 1H), 8.01 (d, 1H), 7.96 (s, 1H), 7.71 (d, 1H), 7.58-7.62 (m, 2H), 7.07-7.36 (m, 5H), 6.66 (d, 1H), 6.25 (dt, 1H), 5.64 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.55 (t, 4H), 3.15 (d, 2H), 2.24-2.32 (m, 14H), 1.88 (t, 12H), 1.56 (p, 2H); reverse phase HPLC (5% to 95% acetonitrile over 25 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=17.1 min; MS m/e 678.7 $(M-H)^-$.

Example 355

N-{4-[4-amino-7-((1E)-3-{4-[3-(1-pyrrolidinyl)propyl]-1-piperazinyl}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

Prepared as the diacetate salt from 1-[3-(1-pyrrolidinyl)propyl]piperazine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.52 (s, 1H), 8.01 (d, 1H), 7.96 (s, 1H), 7.71 (d, 1H), 7.58-7.62 (m, 2H), 7.07-7.36 (m, 5H), 6.66 (d, 1H), 6.23 (dt, 1H), 5.64 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.15 (d, 2H), 2.26-2.39 (m, 16H), 1.88 (s, 6H), 1.59-1.66 (m, 6H); reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=9.4 min; MS m/e 662.5 $(M-H)^-$.

Example 356

N-[2-({(2E)-3-[4-amino-3-(3-methoxy-4-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}phenyl)thieno[3,2-c]pyridin-7-yl]-2-propenyl}amino)ethyl]glycine

Prepared as the acetate salt from N-(2-aminoethyl)glycine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.52 (s, 1H), 8.01 (d, 1H), 8.00 (s, 1H), 7.79 (s, 1H), 7.71 (d, 1H), 7.58-7.62 (m, 2H), 7.07-7.36 (m, 5H), 6.73 (d, 1H), 6.25 (dt, 1H), 5.67 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.20-3.28 (m, 6H), 3.00 (s, 2H), 2.64 (t, 2H), 1.88 (s, 3H); reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=11.0 min; MS m/e 565.7 $(M-H_2O)^+$.

Example 357

N-[4-(4-amino-7-{(1E)-3-[(3S)-3-(dimethylamino)-1-pyrrolidinyl]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

Prepared as the tetraacetate salt from (3S)-N,N-dimethyl-3-pyrrolidinamine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.51 (s, 1H), 8.00 (d, 1H), 7.96 (s, 1H), 7.70 (d, 1H), 7.58-7.61 (m, 2H), 7.07-7.36 (m, 5H), 6.68 (d, 1H), 6.23 (dt, 1H), 5.64 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.18-3.34 (m, 4H), 2.65-2.76 (m, 3H), 2.28-2.50 (m, 2H), 2.10 (s, 6H), 1.85 (s, 12H), 1.59-1.65 (m, 1H); reverse phase HPLC (5% to 95% acetonitrile over 25 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=20.0 min; MS m/e 579.5 $(M-H)^-$.

Example 358

N-{4-[4-amino-7-((1E)-3-{[4-(dimethylamino)phenyl]amino}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide

Prepared from N,N-dimethyl-1,4-benzenediamine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.50 (s, 1H), 7.99 (d, 1H), 7.94 (s, 1H), 7.70 (d, 1H), 7.60 (s, 1H), 7.58 (d, 1H), 7.35 (s, 1H), 7.33 (m, 1H), 7.19 (m, 1H), 7.15 (t, 1H), 7.07 (dd, 1H), 6.74 (d, 1H), 6.62 (m, 4H), 6.33 (m, 1H), 5.62 (br s, 2H), 5.3 (br s, 1H), 4.03 (s, 3H), 3.90 (s, 3H), 3.86 (d, 2H), 2.71 (s, 6H); MS m/e 603.7 $(M+H)^+$ 601.8 $(M-H)^-$.

Example 359

N-[4-(4-amino-7-{(1E)-3-[(4-hydroxycyclohexyl)amino]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

Prepared as the diacetate salt from 4-aminocyclohexanol. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.51 (s, 1H), 8.00 (d, 1H), 7.94 (s, 1H), 7.69 (d, 1H), 7.62 (s, 1H), 7.58 (d, 1H), 7.35 (s, 1H), 7.33 (m, 1H), 7.21 (s, 1H), 7.15 (t, 1H), 7.08 (d, 1H), 6.65 (d, 1H), 6.27 (m, 1H), 5.61 (br s, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.41 (d, 2H), 3.36 (m, 1H), 2.4 (m, 1H), 1.7-1.9 (m, 4H), 1.89 (s, 3H), 1.11 (m, 4H); MS m/e 582.7 $(M+H)^+$ 580.8 $(M-H)^-$.

Example 360

7-[(1E)-3-(diethylamino)-1-propenyl]-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-4-amine

Example 360A

7-[(1E)-3,3-diethoxy-1-propenyl]-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-4-amine

A mixture of Example 176A (250 mg, 0.70 mmol), 4-phenoxyphenylboronic acid (180 mg, 0.84 mmol), $Pd(PPh_3)_4$ (50 mg, 0.04 mmol), and sodium carbonate (150 mg, 1.4 mmol) in 1,2-dimethoxyethane (8 mL) and water (4 mL) was heated to reflux for 15 hours. The mixture was cooled to room temperature and concentrated under reduced pressure. The mixture was extracted with dichloromethane and the extract was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel to provide the desired product (170 mg, 55%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.00 (s, 1H), 7.56 (s, 1H), 7.47 (m, 4H), 7.20 (t, 1H), 7.13 (m, 4H), 6.81 (d, 1H), 6.17 (dd, 1H), 5.67 (br s, 2H), 5.13 (d, 1H), 3.57 (m, 4H), 1.18 (t, 6H); MS m/e 447.3 $(M+H)^+$.

Example 360B

(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]acrylaldehyde

A mixture of Example 360A (170 mg, 0.38 mmol), p-toluenesulfonic acid (10 mg),

acetone (9 mL), and water (1 mL) was stirred for 1.25 hours and concentrated. The residue partioned between saturated aqueous sodium bicarbonate and dichloromethane. The organic layer was dried ($MgSO_4$), filtered, and concentrated to provide the desired product (150 mg). ^1H NMR (DMSO-d_6, 400 MHz) δ 9.66 (d, 1H), 8.32 (s, 1H), 7.89 (d, 1H), 7.68 (s, 1H), 7.47 (m, 4H), 7.20 (t, 1H), 7.14 (m, 4H), 6.65 (dd, 1H); MS m/e 373.3 $(M+H)^+$, 371.1 $(M-H)^-$.

Example 360C

7-[(1E)-3-(diethylamino)-1-propenyl]-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-4-amine

A mixture of Example 360B (30 mg, 0.080 mmol), sodium triacetoxyborohydride (35 mg, 0.16 mmol), 1 drop of acetic acid, and diethylamine (12 mg, 0166 mmol) in 1,2-dichloroethane (2 mL) was stirred for 2 hours at ambient temperature. The mixture was concentrated and the residue was purified by reverse phase chromatography followed by lyophilization to provide the desired product as the acetate salt. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.94 (s, 1H), 7.55 (s, 1H), 7.44 (m, 4H), 7.20 (t, 1H), 7.11 (m, 4H), 6.67 (d, 1H), 6.22 (m, 1H), 5.55 (br s, 2H), 3.28 (d, 2H), 2.52 (q, 4H), 1.87 (s, 3H), 1.00 (t, 6H); MS m/e 430.4 $(M+H)^+$.

Example 361

7-[(1E)-3-({2-[(2R)-1-methyl-2-pyrrolidinyl]ethyl}amino)-1-propenyl]-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-4-amine

The desired product was prepared as the acetate salt by substituting 2-[(2R)-1-methyl-2-pyrrolidinyl]ethanamine for diethylamine in Example 360. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.96 (s, 1H), 7.58 (s, 1H), 7.45 (m, 4H), 7.21 (t, 1H), 7.13 (m, 4H), 6.76 (d, 1H), 6.25 (m, 1H), 5.61 (br s, 2H), 3.54 (d, 2H), 2.95 (m, 1H), 2.71 (m, 2H), 2.24 (s, 3H), 2.16 (m, 2H), 1.89 (s, 3H), 1.85 (m, 2H), 1.35-1.67 (m, 4H); MS m/e 483.4 $(M+H)^+$.

Example 362

2-(1-{(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-2-propenyl}-4-piperidinyl)ethanol

The desired product was prepared as the acetate salt by substituting 2-(4-piperidinyl)ethanol for diethylamine in Example 360. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.94 (s, 1H), 7.55 (s, 1H), 7.46 (m, 4H), 7.20 (t, 1H), 7.12 (m, 4H), 6.64 (d, 1H), 6.21 (m, 1H), 5.56 (br s, 2H), 4.35 (br s, 1H), 3.42 (t, 2H), 3.14 (d, 2H), 2.89 (m, 2H), 1.92 (m, 2H), 1.87 (s, 3H), 1.62 (m, 2H), 1.34 (m, 3H), 1.14 (m, 2H); MS m/e 485.4 $(M+H)^+$.

Example 363

2-[{(2E)-3-[4-amino-3-(4-phenoxyphenyl)thieno[3,2-c]pyridin-7-yl]-2-

propenyl}(ethyl)amino]ethanol

The desired product was prepared as the diacetate salt by substituting 2-(ethylamino)ethanol for diethylamine in Example 360. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.94 (s, 1H), 7.55 (s, 1H), 7.46 (m, 4H), 7.20 (t, 1H), 7.13 (m, 4H), 6.67 (d, 1H), 6.23 (m, 1H), 5.78 (br s, 2H), 3.50 (t, 2H), 3.33 (d, 2H), 2.56 (m, 4H), 1.85 (s, 6H), 1.01 (t, 3H); MS m/e 446.3 $(M+H)^+$.

Example 364

N-(4-{4-amino-7-[(1E)-3-hydroxy-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide

A mixture of Example 176C (30 mg, 0.062 mmol) and sodium borohydride (10 mg, 0.186 mmol) in methanol was stirred at ambient temperature for one hour then concentrated under reduced pressure. The residue was purified by preparative reverse phase HPLC then lyophilized to provide the desired product as the acetate salt. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.51 (s, 1H), 7.99 (d, 1H), 7.97 (s, 1H), 7.69 (d, 1H), 7.62 (s, 1H), 7.58 (m, 1H), 7.35 (s, 1H), 7.33 (t, 1H), 7.21 (t, 1H), 7.15 (t, 1H), 7.08 (d, 1H), 6.70 (d, 1H), 6.36 (m, 1H), 5.62 (br s, 2H), 4.20 (d, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 1.87 (s, 3H); MS m/e 485.4 $(M+H)^+$.

Example 365

tert-butyl 4-{4-amino-7-[(1E)-3-(diethylamino)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenylcarbamate

Example 365A

tert-butyl 4-{4-amino-7-[(1E)-3-oxo-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenylcarbamate

A mixture of Example 294B (1.0g, 2.0 mmol), 2-(3,3-diethoxy-1-propenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (620 mg, 2.4 mmol), $Pd(PPh_3)_4$ (140 mg, 0.12 mmol) and sodium carbonate (640 mg, 6.04 mmol) in 1,2-dimethoxyethane (20 mL) and water (10 mL) was heated to reflux for 15 hours. The mixture was cooled to room temperature and concentrated under reduced pressure. The mixture was extracted with dichloromethane and the extract was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel to provide tert-butyl 4-{4-amino-7-[(1E)-3,3-diethoxy-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenylcarbamate (790 mg) which was then stirred for 12 hours in a mixture of acetone (18 mL) and water (2 mL) containing p-toluene sulfonic acid (35 mg). The solvents were removed under reduced pressure and the residue was partitioned between saturated aqueous sodium bicarbonate and dichloromethane. The organic phase was dried ($MgSO_4$), filtered, and concentrated to provide the desired product

(610 mg).

Example 365B

tert-butyl 4-{4-amino-7-[(1E)-3-(diethylamino)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenylcarbamate

The desired product was prepared by substituting Example 365A for Example 360B in Example 360C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.11 (s, 1H), 7.92 (s, 1H), 7.82 (m, 1H), 7.53 (s, 1H), 7.06 (s, 1H), 6.96 (dd, 1H), 6.65 (d,1H), 6.22 (m, 1H), 5.57 (br s, 2H), 3.84 (s, 3H), 3.28 (d, 2H), 2.54 (q, 4H), 1.48 (s, 9H), 1.00 (t, 6H); MS m/e 483.5 $(M+H)^+$.

Example 366

3-(4-amino-3-methoxyphenyl)-7-[(1E)-3-(diethylamino)-1-propenyl]thieno[3,2-c]pyridin-4-amine

A mixture of Example 365B (425 mg, 0.88 mmol) in acetone (10 mL) and 6N aqueous hydrochloric acid (2 mL) was stirred for 18 hours at ambient temperature then concentrated under reduced pressure. The residue was then purified by preparative reverse phase HPLC to provide the desired product as the diacetate salt. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.89 (s, 1H), 7.39 (s, 1H), 6.82 (s, 1H), 6.73 (s, 2H), 6.20 (m, 1H), 5.65 (br s, 2H), 3.78 (s, 3H), 3.30 (d, 2H), 2.56 (q, 4H), 1.88 (s, 6H), 1.01 (t, 6H); MS m/e 383.4 $(M+H)^+$.

General Procedure for Acylation Reactions

A mixture of Example 366 (50 mg, 0.13 mmol) and pyridine (0.2 mL) in dichloromethane was treated with the appropriate acid chloride (1.2 eq), stirred for 2 hours at ambient temperature, and concentrated. The products were purified by reverse phase chromatography.

The following examples were prepared by this general procedure using the indicated acid chloride.

Example 367

N-(4-{4-amino-7-[(1E)-3-(diethylamino)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-5-bromo-1-methyl-1H-indole-2-carboxamide

Prepared as the diacetate salt from 5-bromo-1-methyl-1*H*-indole-2-carbonyl chloride. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.64 (s, 1H), 7.95 (m, 3H), 7.61 (s, 1H), 7.59 (d, 1H), 7.42 (dd, 1H), 7.31 (s, 1H), 7.19 (d, 1H), 7.06 (dd, 1H), 6.72 (d, 1H), 6.25 (m, 1H), 5.65 (br s, 2H), 4.02 (s, 3H), 3.90 (s, 3H), 3.35 (d, 2H), 2.61 (q, 4H), 1.90 (s, 6H), 1.04 (t, 6H); MS m/e 618, 620 $(M+H)^+$, 616.4, 618.4 $(M-H)^-$.

Example 368

N-(4-{4-amino-7-[(1E)-3-(diethylamino)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1H-indole-2-carboxamide

Prepared as the diacetate salt from 1H-indole-2-carbonyl chloride. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.84 (br s, 1H), 9.52 (s, 1H), 8.00 (d, 1H), 7.95 (s, 1H), 7.66 (d, 1H), 7.61 (s, 1H), 7.47 (d, 1H), 7.39 (s, 1H), 7.23 (t, 1H), 7.19 (d, 1H), 7.08 (m, 2H), 6.68 (d, 1H), 6.25 (m, 1H), 5.63 (br s, 2H), 3.92 (s, 3H), 3.28 (d, 2H), 2.54 (q, 4H), 1.89 (s, 6H), 1.01 (t, 6H); MS m/e 526.5 $(M+H)^+$, 524.5 $(M-H)^-$.

Example 369

N-(4-{4-amino-7-[(1E)-3-(diethylamino)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-benzofuran-2-carboxamide

Prepared as the diacetate salt from 1-benzofuran-2-carbonyl chloride. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.12 (d, 1H), 7.95 (s, 1H), 7.84 (d, 1H), 7.80 (s, 1H), 7.76 (d, 1H), 7.61(s, 1H), 7.53 (m, 1H), 7.38 (t, 1H), 7.23 (d, 1H), 7.09 (dd, 1H), 6.86 (d, 1H), 6.24 (m, 1H), 5.62 (br s, 2H), 3.95 (s, 3H), 3.28 (d, 2H), 2.53 (q, 4H), 1.87 (s, 6H), 1.01 (t, 6H); MS m/e 527.6 $(M+H)^+$, 526.8 $(M-H)^-$.

Example 370

N-(4-{4-amino-7-[(1E)-3-(diethylamino)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-benzothiophene-2-carboxamide

Prepared as the acetate salt from 1-benzothiophene-2-carbonyl chloride. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.92 (br s, 1H), 8.39 (s, 1H), 8.08 (d, 1H), 8.00 (d, 1H), 7.96 (s, 1H), 7.87 (d, 1H), 7.63 (s, 1H), 7.49 (m, 2H), 7.22 (s, 1H), 7.08 (dd, 1H), 6.69 (d, 1H), 6.25 (m, 1H), 5.63 (br s, 2H), 3.92 (s, 3H), 3.28 (d, 2H), 2.53 (q, 4H), 1.89 (s, 3H), 1.01 (t, 6H); MS m/e 543.6 $(M+H)^+$, 541.6 $(M-H)^-$.

Example 371

N-(4-{4-amino-7-[(1E)-3-(diethylamino)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-5-methyl-1H-indole-2-carboxamide

Prepared as the acetate salt from 5-methyl-1H-indole-2-carbonyl chloride. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.71 (s, 1H), 9.47 (s, 1H), 8.01 (d, 1H), 7.96 (s, 1H), 7.61 (s, 1H), 7.44 (s, 1H), 7.36 (d, 1H), 7.29 (s, 1H), 7.19 (s, 1H), 7.07 (m, 2H), 6.69 (d, 1H), 6.25 (m, 1H), 5.64 (br s, 2H), 3.92 (s, 3H), 3.29 (d, 2H), 2.54 (q, 4H), 2.39 (s, 3H), 1.90 (s, 3H), 1.01 (t, 6H); MS m/e 540.6 $(M+H)^+$, 538.6 $(M-H)^-$.

Example 372

N-(4-{4-amino-7-[(1E)-3-(diethylamino)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-5-ethyl-1H-indole-2-carboxamide

Prepared as the diacetate salt from 5-ethyl-1*H*-indole-2-carbonyl chloride. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.72 (br s, 1H), 9.47 (s, 1H), 8.00 (d, 1H), 7.95 (s, 1H), 7.61 (s, 1H), 7.45 (s, 1H), 7.38 (d, 1H), 7.31 (d, 1H), 7.20 (s, 1H), 7.09 (m, 2H), 6.69 (d, 1H), 6.24 (m, 1H), 5.63 (br s, 2H), 3.92 (s, 3H), 3.29 (d, 2H), 2.69 (q, 2H), 2.53 (q, 4H), 1.88 (s, 6H), 1.23 (t, 3H), 1.01 (t, 6H); MS m/e 554.6 $(M+H)^+$, 552.6 $(M-H)^-$.

Example 373

7-[(1E)-3-(diethylamino)-1-propenyl]-3-(3-methoxyphenyl)thieno[3,2-c]pyridin-4-amine

Example 373A

(2E)-3-(4-amino-3-bromothieno[3,2-c]pyridin-7-yl)acrylaldehyde

A mixture of Example 176A (200 mg, 0.56 mmol), p-toluenesulfonic acid (10 mg), acetone (10 mL), and water (1 mL) at ambient temperature was stirred for 16 hours. The mixture was concentrated and washed with sodium bicarbonate (12 mL). The aqueous layer was extracted with dichloromethane/methanol (9:1). The combined organic extracts were concentrated to provide the desired product (160 mg, 0.92 mmol). Reverse phase HPLC (5% to 95% acetonitrile over 25 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=15.5 min.

Example 373B

3-bromo-7-[(E)-3-(diethylamino)-1-propenyl]thieno[3,2-c]pyridin-4-amine

A mixture of Example 373A (260 mg, 0.92 mmol), diethylamine (134 mg, 1.84 mmol), and sodium triacetoxyborohydride (400 mg, 1.84 mmol) was stirred at ambient temperature in dichloroethane (15 mL) for 3 hours, treated with additional diethylamine (400 mg) and sodium triacetoxyborohydride (500 mg), and stirred for 14 hours. The mixture was concentrated, redissolved in dichloromethane (15 mL), and washed with sodium bicarbonate (10 mL). The aqueous layer was extracted with dichloromethane (4 x 15 mL). The combined organic extracts were concentrated and purified by flash column chromatography with dichloromethane/methanol (85:15) to provide the desired product (143 mg, 0.39 mmol): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.94 (s, 1H), 7.87 (s, 1H), 6.66 (br s, 2H), 6.60 (d, 1H), 6.15 (dt, 1H), 3.25 (d, 2H), 2.48-2.50 (m, 4H), 0.99 (t, 6H); reverse phase HPLC (5% to 100% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=8.0 min; MS m/e 341.4 $(M+H)^+$.

Example 373C

7-[(1E)-3-(diethylamino)-1-propenyl]-3-(3-methoxyphenyl)thieno[3,2-c]pyridin-4-amine

A mixture of Example 373B (45 mg, 0.14 mmol), 3-methoxyphenylboronic acid (23 mg, 0.15 mmol), sodium carbonate (28 mg, 0.26 mmol), and $Pd(PPh_3)_4$ (9 mg, 0.008 mmol) was heated to 95 °C for 16 hours in dimethoxy ethylene glycol (2 mL) and water (1 mL). Additional boronic acid (17 mg), $Pd(PPh_3)_4$ (9 mg), and sodium carbonate (20 mg) were added, and the mixture was stirred for another 3 hours. The mixture was concentrated and extracted with dichloromethane (4 x 2 mL). The organic layers were combined, concentrated, and purified by flash column chromatography with dichloromethane/methanol (8:2) to provide the desired product (15 mg, 0.04 mmol). ^1H NMR (DMSO-d_6, 400 MHz) δ 7.94 (s, 1H), 7.54 (s, 1H), 7.45 (t, 1H), 7.01-7.12 (m, 3H), 6.68 (d, 1H), 6.23 (dt, 1H), 5.65 (br s, 2H), 3.81 (s, 3H), 3.29 (d, 2H), 1.01 (t, 6H); reverse phase HPLC (5% to 100% acetonitrile over 25 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=14.2 min; MS m/e 366.4 $(M-H)^-$.

General Procedure for Suzuki Coupling of Northern Domain Followed by Reductive Amination

A mixture of Example 176A (100 mg, 0.28 mmol), sodium carbonate (60 mg, 0.56 mmol), $Pd(PPh_3)_4$ (19 mg, 0.017 mmol), and the appropriate boronate (0.34 mmol) was heated to 95 °C for 16 hours in dimethoxyethylene glycol (4 mL) and water (2 mL), treated with additional boronate (10 mmol), palladium (10 mg), and sodium carbonate (30 mg), stirred for 3 hours, concentrated, and extracted with dichloromethane (4 x 2 mL). The organic extracts werere combined, concentrated, and purified by flash column chromatography with dichloromethane/ethyl acetate (6:4) to provide the coupled product.

A mixture of the coupled product (100 mg), p-toluenesulfonic acid (10 mg), acetone (10 mL), and water (1 mL) was stirred at room temperature for 16 hours, concentrated, and washed with sodium bicarbonate (12 mL). The aqueous layer was extracted with dichloromethane/methanol (9:1) and the combined organic extracts were concentrated to provide the desired aldehydes which were used in the next reaction without further purification.

A mixture of diethylamine (12 mg, 0.166 mmol), sodium triacetoxyborohydride (35 mg, 0.166 mmol) and the aldehyde (0.083 mmol) in 1,2-dichloromethane (2 mL) was stirred for 2 to 72 hours at ambient temperature. The mixture was concentrated and the product purified by normal and/or reverse phase chromatography to provide the desired product.

The following examples were prepared according to this procedure using the boronate indicated:

Example 374

N-(4-{4-amino-7-[(1E)-3-(diethylamino)-1-propenyl]thieno[3,2-c]pyridin-3-yl}phenyl)-1-methyl-1H-indole-2-carboxamide

Example 374A

1-methyl-N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1H-indole-2-carboxamide

A mixture of oxalyl chloride (0.35 mL) and dimethylformamide (1 drop) was added to a solution of 1-methyl-1*H*-2-indolecarboxylic acid (440 mg, 2.51 mmol) in dichloromethane (10 mL). After one hour the mixture was evaporated, dissolved in dichloromethane (10 mL), and added to a mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (500 mg, 2.28 mmol) and diisopropylethylamine (0.35 mL) in dichloromethane (10 mL). After 16 hours the mixture was washed with water (10 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography to provide the desired product (600 mg, 1.60 mmol) after lyophilization: MS m/e 377.4 $(M+H)^+$.

Example 374B

N-(4-{4-amino-7-[(1E)-3-(diethylamino)-1-propenyl]thieno[3,2-c]pyridin-3-yl}phenyl)-1-methyl-1H-indole-2-carboxamide

boronate: Example 374A. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.56 (s, 1H), 7.93-7.98 (m, 3H), 7.10-7.75 (m, 9H), 6.67 (d, 1H), 6.21 (dt, 1H), 5.58 (br s, 2H), 4.02 (s, 3H), 3.22 (d, 2H), 2.48 (q, 4H), 1.00 (t, 6H); reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=10.4 min.; MS m/e 508.6 $(M-H)^-$.

Example 375

N-(4-{4-amino-7-[(1E)-3-(diethylamino)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-benzimidazole-2-carboxamide

Example 375A

1-methyl-1H-benzimidazole-2-carboxylic acid

A suspension of 1-methyl-1H-benzimidazole (5.0 g, 37.83 mmol) in diethyl ether at -78 °C was treated slowly with 1.6M n-butyllithium in hexanes (26 mL, 41.61 mmol) while maintaining the temperature at below -60 °C, and stirred at -78 °C for 30 minutes. Carbon dioxide was bubbled through the reaction solution for 40 minutes. The dry ice bath was then removed to bring the temperature to -5 °C. Concentrated hydrochloric acid (7 mL) was added slowly. The reaction mixture was stirred at -5 °C for 30 minutes, and then water (10 mL) was added. The solid was collected by filtration and dried to remove the excess water to provide

4.8g (72%) of the desired product which was directly used in the next reaction without further purification or analysis.

Example 375B

1-methyl-1H-benzimidazole-2-carbonyl chloride

A suspension of 1Example 375A (0.298 g, 1.69 mmol) in dichloromethane (5 mL) at 0 °C was treated with oxalyl chloride (0.255 g, 1.77 mmol) and 1 drop of DMF. The reaction mixture was stirred for 15 minutes at 0 °C and at room temperature for 4 hours. The solvent was removed under reduced pressure and the residue was dried on the high vacuum. The reaction mix was directly used in the subsequent reaction without further purification or analysis.

Example 375 C

N-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1H-benzimidazole-2-carboxamide

A solution of 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.384 g, 1.54 mmol) in tetrahydrofuran (10 mL) was treated with Example 375B(0.330 g, 1.696 mmol) and diisopropylethyl amine (0.239 g, 1.85 mmol). The reaction mixture was stirred for 18 hours at room temperature under a nitrogen atmosphere, treated with 1N NaOH (5 mL), concentrated, and treated with dichloromethane. The layers were partitioned and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Diethyl ether was added and the solid was collected by filtration to provide 0.220 g (35%) of the desired product. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.184 (s, 1H), 8.4396-8.4197 (d, 1H, J = 7.96 Hz), 7.8453-7.8253 (d, 1H, J = 8 Hz), 7.7614-7.7410 (d, 1H, J = 8.16 Hz), 7.471-7.435 (t, 1H), 7.399-7.367 (m, 2H), 7.306 (s, 1H), 4.226 (s, 3H), 3.995 (s, 3H), 1.315 (s, 12 H); TLC (30% ethyl acetate in heptane) R_f = 0.5.

Example 375D

N-(4-{4-amino-7-[(1E)-3-(diethylamino)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-benzimidazole-2-carboxamide

boronate: N-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1H-benzimidazole-2-carboxamide. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.2 (s, 1H), 8.52 (d, 1H), 8.10 (s, 1H), 7.86 (d, 1H), 7.74-7.79 (m, 3H), 7.38-7.49 (m, 2H), 7.27 (s, 1H), 7.05-7.15 (m, 2H), 6.25 (m, 1H), 4.25 (s, 3H), 3.90-4.02 (m, 5H), 3.18 (q, 4H), 1.28 (t, 6H); reverse phase HPLC (5% to 95% acetonitrile over 10 minutes, 1 mL/min, 254 nm, hypersil HS 100 Å, C18, 5 μm, 250 x 4.6 column) R_t=11.0 min.; MS m/e 539.4 $(M-H)^-$.

General Procedure for Preparation of Amides from Oxalyl Chloride (Synthetic Method 1)

A suspension of the sodium salt of Example 270 (0.050g, 0.096 mmol, prepared by treating Example 270 with 1N NaOH) in dichloromethane (2.0 mL) was treated with oxalyl chloride (0.020 mL, 0.219 mmol) and N,N-dimethylformamide (0.010 mL, 0.129 mmol), stirred at room temperature under nitrogen for 20 minutes, treated dropwise with a 2.0M solution of the appropriate amine in THF (1.0 mL, 2.00 mmol), stirred at ambient temperature for 20 minutes, and concentrated to a dry powder under reduced pressure. The crude material was purified by preparative HPLC using method B described below.

General Procedure for the Preparation of Amides using O-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (Synthetic Method 2)

A mixture of the sodium salt of Example 270 (0.040g, 0.071 mmol, prepared by treating Example 270 with 1N NaOH) in N,N-dimethylformamide (1.00 mL) was treated with diisopropylethylamine (0.060 mL, 0.344 mmol), the appropriate amine (0.230 mmol), O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (0.031g, 0.081 mmol), and hydroxybenzotriazole (0.013g, 0.081 mmol). The reaction was stirred at ambient temperature under an atmosphere of nitrogen for 18 hours. The products not containing protecting groups were purified by preparative HPLC using method A or B. The products containing a t-butoxycarbonyl protected amines were concentrated to dry powders under reduced pressure and deprotected using the conditions described below.

General Procedure for the Deprotection of N-tert-Butoxycarbonyl Protected Amines from Synthetic Method 2

A mixture of the protected coupling product, trifluoracetic acid (0.30 mL), and dichloromethane (0.90 mL) was stirred at ambient temperature for 2 hours and concentrated. The crude material was purified by preparative HPLC using method A or B.

General Procedure for the Saponification of Ester-Containing Amines

A mixture of the ester (0.016 mmol) in tetrahydrofuran (0.30mL) and methanol (0.30 mL) was treated with 2N NaOH (0.03 mL, 0.60 mmol). The reaction was stirred at room temperature for 18 hours before the solvents were removed under reduced pressure. The compound was extracted with 1:1 tetrahydrofuran / ethyl acetate (3 x 1mL). The combined extracts were dried (Na_2SO_4, 20 mg), filtered, and concentrated.

Preparative HPLC Conditions (Purification Method A)

Micromass, Hypersil BDS C18, 5 μm, 100 x 21.2 mm; 25%-75% acetonitrile – 50 mM ammonium acetate over 7 min, 100% acetonitrile for 2 min, 100% - 25% acetonitrile –

50 mM ammonium acetate over 1.5 min, 25 mL/min.

Preparative HPLC conditions (Purification Method B)

Hyperprep HS C18, 8 μm, 250 x 21.2 mm; 20% acetonitrile- 50 mM ammonium acetate over 1 min, 20-100% acetonitrile- 50 mM ammonium acetate for 24 min, 100% acetonitrile for 5 min, 20 mL/min.

LCMS (Analytical Method 1)

Agilent HP 1100, Genesis C18, 33 x 4.6 mm, 4 μm. Flow rate: 2.0 mL /min. Mobile phase: acetonitrile / 5mM ammonium acetate. Gradient: 5%- 95% acetonitrile - 5 mM ammonium acetate over 3.5 min, 95- 100% acetonitrile- 5 mM ammonium acetate over 1.0 min., 5% acetonitrile- 5 mM ammonium acetate over 0.5 min. Total run time 5 min.

LCMS (Analytical Method 2)

Finnigan Advantage LCQ-MS, Genesis C18, 30 x 4.6 mm, 3 μm. Flow rate: 0.8 mL/min. Mobile phase: acetonitrile/ 10mM ammonium acetate. Gradient: 30%- 95% acetonitrile - 10 mM ammonium acetate over 3.0 min, hoursold 1.5 min 95% acetonitrile- 10 mM ammonium acetate, : 95%- 30% acetonitrile - 10 mM ammonium acetate over 0.5 min, 30% acetonitrile - 10 mM ammonium acetate over 1 min. Total run time 6 min.

The following examples were prepared using the above methods:

Example	Final Product	Starting Amine	Yield (%)	R_t (min)	m/z $(M+H)^+$	Methods Used (Synthetic, Purification, Analytical)
376	N-(4-{4-amino-7-[(1E)-3-({2-[bis(2-hydroxyethyl)amino]-ethyl}amino)-3-oxo-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide	2-[(2-aminoethyl)(2-hydroxyethyl)-amino]ethanol	55.0	2.37	629.0	2,1,A

377	N-{4-[4-amino-7-((1E)-3-oxo-3-{[3-(2-oxo-1-pyrrolidinyl)-propyl]amino}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	1-(3-aminopropyl)-2-pyrrolidinone	45.7	2.76	623.0	2,1,A
378	N-(4-{4-amino-7-[(1E)-3-({3-[(2R)-2-methyl-1-piperidinyl]propyl}amino)-3-oxo-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide	3-[(2R)-2-methyl-1-piperidinyl]-1-propanamine	54.9	2.72	637.2	2,1,A
379	N-{4-[4-amino-7-((1E)-3-{[2-(diisopropylamino)ethyl]amino}-3-oxo-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	N,N-diisopropyl-1,2-ethanediamine	46.0	2.68	625.2	2,1,A
380	N-(4-{4-amino-7-[(1E)-3-({2-[ethyl(3-methylphenyl)amino]-ethyl}amino)-3-oxo-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide	N-(2-aminoethyl)-N-ethyl-N-(3-methylphenyl)-amine	28.0	3.76	659.0	2,1,A
381	N-{4-[4-amino-7-((1E)-3-{[3-(dimethylamino)-2,2-dimethylpropyl]amino}-3-oxo-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	N,N,2,2-tetramethyl-1,3-propanediamine	47.5	2.67	611.2	2,1,A
382	N-{4-[4-amino-7-((1E)-3-{[3-(4-methyl-1-piperidinyl)propyl]amino}-3-oxo-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	3-(4-methyl-1-piperidinyl)-1-propanamine	44.3	2.70	637.2	2,1,A

383	N-{4-[4-amino-7-((1E)-3-{[3-(dimethylamino)propyl]amino}-3-oxo-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	N,N-dimethyl-1,3-propanediamine	48.2	2.46	583.2	2,1,A
384	N-[4-(4-amino-7-{(1E)-3-[(2-hydroxyethyl)amino]-3-oxo-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide	2-aminoethanol	39.8	2.63	542.0	2,1,A
385	N-{4-[4-amino-7-((1E)-3-{[2-(dimethylamino)ethyl]amino}-3-oxo-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	N,N-dimethyl-1,2-ethanediamine	50.5	2.43	569.2	2,1,A
386	N-[4-(4-amino-7-{(1E)-3-[(3-hydroxypropyl)amino]-3-oxo-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide	3-amino-1-propanol	40.5	2.68	556.2	2,1,A
387	N-{4-[4-amino-7-((1E)-3-{[3-(1H-imidazol-1-yl)propyl]amino}-3-oxo-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	3-(1H-imidazol-1-yl)-1-propanamine	42.1	2.49	606.0	2,1,A
388	N-{4-[4-amino-7-((1E)-3-{[(2S)-2-(dimethylamino)propyl]amino}-3-oxo-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	N-[(1S)-2-amino-1-methylethyl]-N,N-dimethylamine	50.2	2.40	583.2	2,1,A

389	N-{4-[4-amino-7-((1E)-3-oxo-3-{[3-(1-pyrrolidinyl)propyl]amino}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	3-(1-pyrrolidinyl)-1-propanamine	44.2	2.48	609.2	2,1,A
390	N-{4-[4-amino-7-((1E)-3-{[3-(4-morpholinyl)propyl]amino}-3-oxo-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	3-(4-morpholinyl)-1-propanamine	32.5	2.24	625.0	2,1,A
391	N-{4-[4-amino-7-((1E)-3-{[1-(2,6-dimethoxybenzyl)-4-piperidinyl]amino}-3-oxo-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	1-(2,6-dimethoxy-benzyl)-4-piperidinamine	27.0	2.80	731.0	2,1,A
392	N-(4-{4-amino-7-[(1E)-3-({[(2R)-1-ethyl-2-pyrrolidinyl]methyl}amino)-3-oxo-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide	[(2R)-1-ethyl-2-pyrrolidinyl]-methylamine	40.6	2.54	609.2	2,1,A
393	N-[4-(4-amino-7-{(1E)-3-[(1-benzyl-4-piperidinyl)amino]-3-oxo-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide	1-benzyl-4-piperidinamine	38.0	2.71	671.0	2,1,A
394	N-(4-{4-amino-7-[(1E)-3-({[1-(2-methoxyphenyl)-4-piperidinyl]methyl}amino)-3-oxo-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-	[1-(2-methoxyphenyl)-4-piperidinyl]-methylamine	21.9	3.51	701.0	2,1,A

	indole-2-carboxamide					
395	N-{4-[4-amino-7-((1E)-3-{[2,3-dihydroxypropyl]amino}-3-oxo-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	3-amino-1,2-propanediol	37.5	2.51	572.0	2,1,A
396	N-{4-[4-amino-7-((1E)-3-{[3-(diethylamino)propyl]amino}-3-oxo-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	N,N-diethyl-1,3-propanediamine	31.3	2.56	611.2	2,1,A
397	N-{4-[4-amino-7-((1E)-3-{[2-(diethylamino)ethyl]amino}-3-oxo-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	N,N-diethyl-1,2-ethanediamine	46.0	2.60	597.2	2,1,A
398	N-(4-{4-amino-7-[(1E)-3-({[(2S)-1-ethyl-2-pyrrolidinyl]methyl}amino)-3-oxo-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide	[(2S)-1-ethyl-2-pyrrolidinyl]-methylamine	44.2	2.64	609.2	2,1,A
399	N-{4-[4-amino-7-((1E)-3-{[2-(dimethylamino)-1-methylethyl]amino}-3-oxo-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	N-[2-aminopropyl]-N,N-dimethylamine	46.0	2.49	583.2	2,1,A

400	N-{4-[4-amino-7-((1E)-3-oxo-3-{[2-(1-pyrrolidinyl)ethyl]amino}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	2-(1-pyrrolidinyl)-ethanamine	43.1	2.53	595.2	2,1,A
401	N-{4-[4-amino-7-((1E)-3-oxo-3-{[2-(2-oxo-1-imidazolidinyl)ethyl]amino}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	1-(2-aminoethyl)-2-imidazol-idinone	27.9	2.60	610.0	2,1,A
402	N-{4-[4-amino-7-((1E)-3-{[3-(4-methyl-1-piperazinyl)propyl]amino}-3-oxo-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	3-(4-methyl-1-piperazinyl)-1-propanamine	50.1	2.39	638.2	2,1,A
403	N-[4-(4-amino-7-{(1E)-3-[1-azabicyclo[2.2.2]oct-3-ylamino]-3-oxo-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide	quinuclidin-3-amine	8.1	2.52	607.0	2,1,A
404	N-(4-{4-amino-7-[(1E)-3-({2-[1-methyl-2-pyrrolidinyl]ethyl}amino)-3-oxo-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide	2-[1-methyl-2-pyrrolidinyl]-ethanamine	48.9	2.5	609.0	2,1,A
405	N-{4-[4-amino-7-((1E)-3-{[2-(2,4-dioxo-1,3-thiazolidin-3-yl)ethyl]amino}-3-oxo-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	3-(2-aminoethyl)-1,3-thiazolidine-2,4-dione	30.0	2.97	641.0	2,1,A

406	N-{4-[4-amino-7-((1E)-3-{[2-(1-methyl-1H-pyrrol-2-yl)ethyl]amino}-3-oxo-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	2-(1-methyl-1H-pyrrol-2-yl)ethanamine	30.5	3.27	605.0	2,1,A
407	N-(4-{4-amino-7-[(1E)-3-({2-[methyl(phenyl)amino]-ethyl}amino)-3-oxo-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide	N-(2-aminoethyl)-N-methyl-N-phenylamine	33.6	3.52	631.0	2,1,A
408	N-{4-[4-amino-7-((1E)-3-{[3-(methylamino)propyl]amino}-3-oxo-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	tert-butyl 3-aminopropyl-(methyl)-carbamate	64.7	2.42	569.0	2,1,A
409	N-(4-{4-amino-7-[(1E)-3-oxo-3-({2-[2-piperidinyl]ethyl}amino)-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide	tert-butyl 2-(2-aminoethyl)-1-piperidine-carboxylate	43.1	2.6	609.0	2,1,A
410	N-{4-[4-amino-7-((1E)-3-{[2-(methylamino)ethyl]amino}-3-oxo-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	tert-butyl 2-aminoethyl-carbamate	55.1	2.41	555.0	2,1,A
411	N-{4-[4-amino-7-((1E)-3-oxo-3-{[(3R)-3-pyrrolidinylmethyl]amino}-1-propenyl)thieno[3,2-c]pyridin-3-yl]-2-methoxyphenyl}-1-methyl-1H-indole-2-carboxamide	tert-butyl (3S)-3-(aminomethyl)-1-pyrrolidine-carboxylate	66.5	2.42	581.0	2,1,A

412	N-{(2E)-3-[4-amino-3-(3-methoxy-4-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}phenyl)-thieno[3,2-c]pyridin-7-yl]-2-propenoyl}glycinamide (acetate salt)	glycinamide	41.0	2.47	555.1	2,2,B
413	N-(4-{4-amino-7-[(1E)-3-amino-3-oxo-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide (acetate salt)	ammonium hydroxide	21.0	2.92	498.4	1,2,B
414	N-(4-{4-amino-7-[(1E)-3-(methylamino)-3-oxo-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide (acetate salt)	methylamine	22.0	3.1	512.3	1,2,B
415	N-(4-{4-amino-7-[(1E)-3-(dimethylamino)-3-oxo-1-propenyl]thieno[3,2-c]pyridin-3-yl}-2-methoxyphenyl)-1-methyl-1H-indole-2-carboxamide	N,N-dmethylamine	21.0	3.5	526.4	1,2,B
416	ethyl N-{(2E)-3-[4-amino-3-(3-methoxy-4-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}phenyl)-thieno[3,2-c]pyridin-7-yl]-2-propenoyl}-β-alaninate	ethyl β-alaninate	44.0	3.22	598.3	2,2,B
417	ethyl 4-({(2E)-3-[4-amino-3-(3-methoxy-4-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}phenyl)-thieno[3,2-c]pyridin-7-yl]-2-propenoyl}amino)butanoate	ethyl 4-aminobutanoate	37.0	3.5	612.5	2,2,B

418	N-{(2E)-3-[4-amino-3-(3-methoxy-4-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}phenyl)-thieno[3,2-c]pyridin-7-yl]-2-propenoyl}-β-alanine (sodium salt)	ethyl β-alaninate	10.0	2.1	570.4	2,2,B
419	4-({(2E)-3-[4-amino-3-(3-methoxy-4-{[(1-methyl-1H-indol-2-yl)carbonyl]amino}phenyl)-thieno[3,2-c]pyridin-7-yl]-2-propenoyl}amino)butanoic acid (sodium salt)	ethyl 4-aminobutanoate	81.0	2.12	584.5	2,2,B

Example 420

N-[4-(4-amino-7-{(1E)-3-[4-(2-hydroxyethyl)-1-piperazinyl]-1-propenyl}thieno[3,2-c]pyridin-3-yl)-2-methoxyphenyl]-1-methyl-1H-indole-2-carboxamide

A mixture of Example 176C (40 mg, 0.083 mmol), sodium triacetoxyborohydride (35 mg, 0.166 mmol) and 2-(1-piperazinyl)ethanol (0166 mmol) in 1,2-dichloromethane (2 mL) was stirred for 2 to 72 hours at ambient temperature. The mixture was concentrated and the residue was purified by chromatography to provide the desired product as the diacetate salt. ^{1}H NMR (DMSO, 400 MHz) δ 9.50 (s, 1H), 8.00 (d, 1H), 7.97 (s, 1H), 7.71 (d, 1H), 7.61 (m, 2H), 7.36 (m, 2H), 7.20 (s, 1H), 7.15 (t, 1H), 7.05 (d, 1H), 6.70 (d, 1H), 6.25 (m, 1H), 5.6 (bs, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.47 (t, 2H), 3.4 (m, 4H), 3.15 (d, 2H), 2.5 (m, 4H), 2.45 (t, 2H), 1.88 (s, 6H); MS m/e 597.5 $(M+H)^+$, 595.5 $(M-H)^-$.

It will be evident to one skilled in the art that the present invention is not limited to the foregoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing examples, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.